Guidance for Industry and for FDA Reviewers

Intraocular Lens Guidance Document

Draft Guidance – Not for Implementation

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Intraocular and Corneal Implants Branch
Division of Ophthalmic Devices
Office of Device Evaluation

Preface

Public Comment:

For 90 days following the date of publication in the Federal Register of the notice announcing the availability of this guidance, comments and suggestions regarding this document should be submitted to the Docket No. assigned to that notice, Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852.

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I. Introduction

A. Scope - All of the sections of this guidance document are applicable to all intraocular lenses (IOLs) intended for placement in the anterior segment of the eye, with the exception of the clinical investigations section of this guidance which is specific to the clinical investigations of anterior and posterior chamber monofocal IOLs for the correction of aphakia and the optical section of this document which is specific to the evaluation of monofocal IOLs.

B. Definitions - The definitions in ISO/ FDIS 11979-1 (see Annex F concerning availability) apply. Some definitions which may be unique to that document are reproduced here.

body -
Central part of the intraocular lens incorporating the optic.

finished intraocular lens lot -
All units of an intraocular lens that have undergone a single series of manufacturing operations, including the sterilization operation and which are identified on a single device history record.

haptic -
Nonoptical, generally peripheral, component of an intraocular lens.

intraocular lens model -
Identification by which the features of an intraocular lens, including its body (e.g., body diameter, optic diameter, optic shape factor) and its loops (e.g., configuration, caliber, angulation), and the material(s) used in its construction, have been fully specified.

NOTE - Any significant change in the specification of the materials (including their formulation or synthesis procedures) will result in it being considered a new model.

level A/B modification -
Tier A/B modification.

loop -
Peripheral extension of the body, serving to position the lens in the eye.

NOTE - Loops are parts of the haptic, or may be the haptic.

lost to follow-up -
Subjects for whom the final case reporting form is overdue and who cannot be contacted despite reasonably extensive written and telephone follow-ups to determine their final clinical outcomes. This category does not include subjects who died.

optic -
Image forming, generally central, component of an intraocular lens. A small optic is defined as being less than 5.5 mm in diameter at any meridian.

optic, clear -
Diameter of circle concentric with the optical axis of an intraocular lens containing only features of the intraocular lens belonging to the optical design. May be part of the optic or equivalent to the optic.

parent intraocular lens model -
An intraocular lens model that a sponsor has qualified based on a clinical investigation of at least 100 subjects and which has either received prior PMA approval or has met the requirements of all Parts of ISO 11979.

ridge -
A protuberance added to the posterior optic surface of the IOL to act as a spacer between the posterior optic surface and the posterior capsule.

sagitta -
Distance between the planes, normal to the optical axis, which contact the most anterior and the most posterior point of an uncompressed intraocular lens.

serious adverse event -
In addition to the definition of adverse event in ISO 14155, an adverse event that is potentially sight threatening is a serious adverse event. This is consistent with the definition of serious adverse event on FDA Form 3500 that is used for reporting serious adverse events and product problems with human drug and biologic products and devices (FR Vol. 58, No. 105, pp. 31596-31614).

C. Abbreviations

AC - angle of contact

ASTM - American Society for Testing and Materials

D - diopter

DIS - draft international standard

ECH - ethylene chlorohydrin

ELP - effective lens position

EO - ethylene oxide

IOL - intraocular lens

IDE - investigational device exemption

ISO - International Organization for Standardization

LFB - lower force boundary

MEM - minimum essential medium

MTF - modulation transfer function

PDP - product development protocol

PMA - premarket approval application

PMMA - polymethylmethacrylate

S.E.M. - standard error of the mean

$\mathbf{T_a}$ - temperature used in accelerated study

$\mathbf{T_0}$ - typical storage temperature

UFB - upper force boundary

USP - United States Pharmacopeia

II. Biocompatibility Testing

A. General

Tests should be conducted on the finished product as marketed, or on material that has undergone the same manufacturing and sterilization processes as the IOLs. The test methods specified below are suggested methods. Alternative methods are permitted if appropriately validated. The omission of certain tests should be justified with a valid scientific argument/rationale.

B. Extracts

In tests that are conducted on material extracts, testing should be conducted with two different extractants, one of which is an aqueous solution, e.g., physiological saline (sponsor should define formulation), and the other a lipophilic or dipolar solvent, under conditions as described in ISO/FDIS 11979-5, Annex A. See USP 23, <88>, 1995, for examples of acceptable extractants.

Extraction for cytotoxicity testing is an exception which should be performed according to ISO 10993-5, Test for Cytotoxicity, In Vitro Methods. The extractant(s) used shall be appropriate for the cytotoxicity test protocol(s).

C. Biocompatibility Tests

For IOL materials, all biocompatibility tests listed below should be performed.

1. Cytotoxicity -

Cytotoxicity testing should be carried out in accordance with the requirements of ISO 10993-5.

All of the following cytotoxicity tests are recommended to be performed:

Test	Desired Result
Agar Diffusion Test (Direct Contact)	Non-cytotoxic
Agar Diffusion Test (Extracts)	Non-cytotoxic
Inhibition of Cell Growth	Non-inhibitory
MEM Elution	Non-cytotoxic

Sponsors should provide a scientific rationale for the exclusion of any of the tests.

2. Genotoxicity -

Testing for genotoxic potential should be conducted using two extractants as outlined in Annex D of ISO/FDIS 11979-5, in accordance with ISO 10993-3.

The results should show the material to be non-genotoxic. Otherwise, additional genotoxicity and/or carcinogenicity testing will be necessary.

3. Maximization Sensitization Test -

Testing for sensitization potential should be conducted as outlined using two extractants as outlined in Annex E of ISO/FDIS 11979-5, in accordance with ISO 10993-10.

The results should demonstrate a lack of sensitization potential.

4. Non-Ocular Animal Implantation Test -

This test should be performed in order to demonstrate the tissue tolerance of the test material. Testing should be conducted in accordance with Annex F of ISO/FDIS 11979-5.

The results should demonstrate tolerance of the tissue material.

5. Ocular Implantation Test -

This test should be performed in order to demonstrate the tolerance of the test material after implantation into the animal eye. Testing should be conducted in accordance with Annex F of ISO/FDIS 11979-5.

The results should demonstrate that the test material is well tolerated after implantation into the animal eye.

FDA will consider requests for waivers from the ocular implantation test, provided that:

a. the sponsor provides a valid scientific rationale for omitting the test;
b. the material is chemically identical to a material that has been proven safe and effective as an implant in the human eye (e.g., certain polymethylmethacrylates (PMMAs)); and,
c. the material is derived from the same source as a material proven safe and effective as an implant in the human eye.

6. Nd:YAG Laser Test -

Testing should be conducted as outlined in Annex C of ISO/FDIS 11979-5.

7. Test of Extractables and Hydrolytic Stability

Testing should be conducted as outlined in Annex A of ISO/FDIS 11979-5.

8. Test of Extractables by Exhaustive Extraction -

Exhaustive extraction in an appropriate solvent should be performed to swell the polymer for determination of absolute levels of any free monomers, UV absorber or contaminants. A suggested method for PMMA may be found in Annex A of ANSI Z80.7 1994 or Annex B of ISO/DIS 11979-6.

9. Test for Photostability -

Testing should be conducted as outlined in Annex B of ISO/FDIS 11979-5.

III. Optical Testing

A. General

All tests should be performed on the finished product as marketed. The test methods specified below are suggested methods. Alternative methods are permitted if appropriately validated. Additionally, any validated procedures that ensure that IOLs are within the tolerances specified may be used as quality control (see Manufacturing/ Quality Control).

B. Clear Optic Diameter

The diameter of the clear lens optic with refractive power should be greater than or equal to 4.25 mm. Components such as positioning holes and haptics should not infringe on this minimum diameter.

C. Dioptric Power

When determined by one of the methods described or referenced in Annex A of ISO/FDIS 11979-2, the dioptric power should be within the tolerance limits specified in Table 1 in all meridians.

Table 1 - Tolerances on dioptric power

Nominal dioptric power range (D)	Tolerance on dioptric power (D)
0 to ≤ 15	± 0.3
> 15 to ≤ 25	± 0.4
> 25 to ≤ 30	± 0.5
> 30	± 1.0

Note 1 - Astigmatism is implicitly limited by the requirement that dioptric power be within the tolerance limits of Table 1 in all meridians. The demand on imaging quality also prevents excessive astigmatism.

Note 2 - The tolerances listed in Table 1 represent the combined manufacturing and measurement tolerances around the nominal power. Manufacturers should set their manufacturing tolerances tighter than those listed in Table 1 to meet this combined tolerance. Sponsors are encouraged to provide the mid-range IOL powers in 0.5 D increments to minimize the deviation between the available power and the power required for a specific patient. The power should be determined from the paraxial focal length to prevent errors which may become significant at the higher IOL powers.

Note 3 - The ranges listed in Table 1 apply to positive as well to negative dioptric powers.

D. Imaging Quality

The resolution efficiency of an IOL should be no less than 60% of the diffraction limited cut-off spatial frequency when determined in air according to the methods established in Annex B of ISO/FDIS 11979-2. In addition, the image should have minimal aberrations other than normal spherical aberration.

Alternatively, the MTF requirement given in ISO/FDIS 11979-2 may be used, especially in those cases where the resolution in air requirement cannot be met. The system of model eye with IOL (described in Annex C of ISO/FDIS 11979-2) should exhibit an MTF value greater than 0.43 at 100 c/mm or 70% of the calculated maximum attainable for the design, whichever is the smaller, but always greater than 0.25.

Note - The manufacturer should demonstrate that the entire range of powers of a model

requested for commercial distribution meets this specification.

E. Spectral Transmittance

For each type of IOL, the spectral transmittance in the range 300 nm to 800 nm should be available for the IOL with a dioptric power of 20 D or its equivalent. The spectrum should be recorded with a spectrophotometer using a 3 mm aperture. The spectrophotometer should have a band-width of not more than 5 nm and be accurate to ± 2% transmittance.

The sample should be either an actual IOL or a flat piece of the IOL optic material having an average thickness equal to that of the central 3 mm of the 20 D IOL, and that has undergone the same production treatment as the finished IOL, including sterilization. IOLs made of materials that change transmittance properties in situ should be measured with the IOL under simulated in situ conditions. Additional guidance may be found in ISO 8599 and ISO/FDIS 11979-2 (with the exception that the maximum wavelength measured is 800 nm and not 1200 nm).

F. Lenses in the Extended Power Range

For lenses manufactured in powers greater than + 34 D or less than + 4 D, the manufacturer should identify to FDA the power range requested for commercial distribution and validation that lenses in this range of powers meet the optical requirements described above. Additionally, if the manufacturer chooses optical performance criteria based upon calculated (rather than measured) MTF response, the calculated MTF values should be validated. One acceptable validation method is to compare the measured MTF values for high quality IOLs in the 10 - 20 diopters range (and therefore very close to the diffraction limited performance) to the calculated values generated by the software.

For anterior chamber IOLs, an analysis should be performed to determine the position of the anterior surface of the IOL at the extremes of the extended power range at the minimum recommended overall diameter in relation to the position of the corneal endothelial layer in a typical anterior chamber. Any indication of insufficient clearance may require restrictions on anterior chamber depth in a warning section of the labeling for the IOL or may restrict the power range for that model.

IV. Mechanical Testing and Dimensional Tolerances

A. General

All tests should be performed on the finished product as is planned to be marketed. IOLs whose dimensions are not appreciably affected by the temperature and aqueous environment in situ (e.g., PMMA IOLs) should be evaluated at a documented controlled temperature. For all other IOLs, properties should be determined at in situ conditions with the temperature tolerance of ± 2 °C. The precise composition of the solution used should be reported in all cases.

B. Dimensions

Dimensions for which tolerances are given below are to be specified in the manufacturer's design documentation. The tolerances provided are recommendations only, and sponsors may propose other valid tolerances. The sponsor should validate that their production meets their tolerances to appropriate statistical levels. Some dimensions are to be included in the labeling of the product. These requirements are also outlined in ISO/FDIS 11979-3.

1. The recommended tolerance on the overall diameter should be as follows:

   ± 0.20 mm - for all types of IOLs, except multi-piece posterior chamber IOLs
   ± 0.30 mm - for multi-piece posterior chamber IOLs

   NOTE - For symmetrically designed IOLs with two haptics, the overall diameter equals the distance between haptic vertices.

2. The recommended tolerance on the vault height should be as follows:

   ± 0.15 mm - for anterior chamber IOLs
   ± 0.35 mm - for posterior chamber IOLs with polypropylene loop(s)
   ± 0.25 mm - for other IOLs

3. The recommended tolerance on the sagitta should be as follows:

   ± 0.25 mm - for anterior chamber IOLs
   ± 0.45 mm - for posterior chamber IOLs with polypropylene loop(s)
   ± 0.35 mm - for other IOLs

4. The recommended tolerance on the optic should be ± 0.10 mm.

5. The recommended tolerance on the dimensions of the body should be ± 0.10 mm. For ellipsoid IOLs, the dimensions of the body should be reported as (short axis) x (long axis).

6. The recommended tolerance on the diameter of the positioning hole should be (+ 0.05/- 0.00) mm.

C. Mechanical Testing

Mechanical requirements given below should be specified in the manufacturer's design documentation. The sponsor should validate that their production meets these tolerances. If dioptric power affects the property tested, low, medium and high dioptric power IOL lots should be used. The minimum sample size for each test should be 10 IOLs per lot per power. The lots should be representative of finished IOLs being marketed. Testing should be performed on finished product (i.e., after sterilization/ aeration).

1. Optic decentration -

The sum of the mean optic decentration and 2 standard deviations of the optic decentration should not exceed 10% of the clear optic at the diameters used for compression testing (i.e. 10 mm and/or 11 mm). If it does exceed 10% of the clear optic diameter, it should be demonstrated that this amount of decentration does not have a significant impact on IOL performance by demonstrating that the MTF optical specification is still met with this amount of decentration of the optic for the whole range of powers being marketed. A suggested method for decentration testing is described in ISO/FDIS 11979-3 Annex C. A suggested method for MTF testing is described in ISO/FDIS 11979-2 Annex C.

2. Optic tilt -

The sum of the mean optic tilt and 2 standard deviations of the optic tilt should not exceed 5° at the diameters used for compression testing (i.e. 10 mm and/or 11 mm). If it does exceed 5°, it should be demonstrated that this amount of tilt does not have a significant impact on IOL performance by demonstrating that the MTF optical specification is still met with this amount of tilt of the optic for the whole range of powers being marketed. A suggested method for tilt testing is described in ISO/FDIS 11979-3 Annex D. A suggested method for MTF testing is described in ISO/FDIS 11979-2 Annex C.

3. Loop pull strength -

All loops of an IOL design should be able to withstand a force of 0.25 N before becoming detached from the optic. A suggested method for loop pull strength testing is described in ISO/FDIS 11979-3 Annex H.

4. Dynamic fatigue durability -

All loops, on IOLs designs where the loop will be compressed when implanted, should be capable of withstanding, without being severely damaged or breaking, 250,000 cycles of near-sinusoidal deformation of ± 0.25 mm at a frequency between 1 Hz and 10 Hz around the compressed distance defined below:

- for IOLs intended for capsular bag placement, at a compressed distance of 5.0 mm between the testing plate and the center of the optic
- for IOLs intended for sulcus placement, at a compressed distance of 5.5 mm between the testing plate and the center of the optic;
- for IOLs intended for both capsular bag and sulcus placement, at a compressed distance of 5.0 mm between the testing plate and the center of the optic; and
- for anterior chamber IOLs, at a compressed distance corresponding to half the minimum and maximum intended compressed diameters as recommended by the manufacturer in the product literature between the testing plate and the center of the optic.

NOTE - The frequency may be adjusted depending on how well sinusoidal behavior of the material is achieved (i.e., if it is verified that the loop follows the testing plate without lag at all times).

A suggested method for dynamic fatigue durability testing is described in ISO/FDIS 11979-3 Annex G with the additional requirement that the surface and bulk homogeneity characteristics regarding the appearance of fractures and/or stress lines in the loops at the points of stress concentration in the test be described.

5. Folding/Injection testing -

IOLs which are folded and/or delivered from an injector system for implantation should be evaluated with all the folding instruments/injector systems that a sponsor includes as recommended for the IOL. There should be no change in the optical and physical properties of the IOL as a result of the folding/delivery. Recommended testing is outlined below.

a. Dioptric power and imaging quality as outlined in Section III of this guidance
b. Overall diameter and sagitta if the loops are engaged/stressed during folding and/or delivery
c. Visual inspection of optics and loops
d. Evaluation of the fold recovery time
e. Evaluation of acceptable amount of time for which the IOL may remain folded; testing should be done for a minimum of three minutes. This information shall be included in the labeling. If testing is performed for twenty minutes or longer, no time limit is needed for the labeling.

Testing should be performed on at least ten lenses each of both the highest and lowest powers with recommended lubricating solutions (i.e., viscoelastics or saline). The characteristics of the lens post- folding/delivery should be within the final lens product specifications by 24 (± 2) hours after folding/injection.

6. Surface and bulk homogeneity -

The IOL should be essentially free from surface and bulk defects and all edges should appear smooth when viewed at 10x magnification with a stereo microscope using optimal lighting conditions.

Anterior chamber IOLs should appear smooth when viewed under SEM at 50x magnification.

D. Mechanical Characterization

The tests described below should be used to characterize the mechanical characteristics associated with a sponsor's design. They should be used during the initial design validation for an IOL model and to determine the clinical requirements necessary for modifications of that design.

1. Compression force -

The compression force should be measured as follows:

- for IOLs intended for capsular bag placement, at a diameter of 10 mm
- for IOLs intended for sulcus placement, at a diameter of 11 mm

- for IOLs intended for both capsular bag and sulcus placement, both at a diameter of 10 mm and at a diameter of 11 mm
- for anterior chamber IOLs, at the minimum and maximum intended compressed diameters as recommended by the manufacturer in the package insert.

A suggested method for compression force testing is described in ISO/FDIS 11979-3 Annex A.

2. Compression force decay -

The compression force decay should be measured at the same diameters that were used for the measurement of compression force after 24 hours in compression at each compressed diameter under in situ conditions. A suggested method for compression force decay testing is described in ISO/FDIS 11979-3 Annex F.

3. Axial displacement in compression -

The axial displacement in compression should be measured and reported at the same diameters that were used for the measurement of compression force.

For anterior chamber IOLs only, the vault height and the sagitta in the compressed state at the minimum and maximum intended compressed diameters should be given for a 20 diopter IOL and for both the dioptric powers at which the edge and center sagitta are the greatest.

An analysis should be performed for anterior chamber lenses to determine the position of the anterior surface of the IOL at its minimum recommended overall diameter in relation to the position of the corneal endothelial layer in a typical anterior chamber. Any indication of insufficient clearance will require restrictions on anterior chamber depth in a warning section of the labeling for the IOL.

A suggested method for axial displacement in compression testing is described in ISO/FDIS 11979-3 Annex B.

4. Angle of contact -

The angle of contact (an approximation of the total haptic contact with the supporting ocular tissue) should be measured at the same diameters that were used for the measurement of compression force. A suggested method for angle of contact in compression testing is described in ISO/FDIS 11979-3 Annex E.

E. Mechanical Data Analysis

The data from the mechanical characterization tests above (except axial displacement in compression) may be used to determine if a modified IOL is a Level A modification of a parent IOL. Either of the two methods of analysis described in ISO/FDIS 11979-3 Annex J may be used for this purpose:

- comparison of the modified model to a single parent model; or
- comparison of a modified model to multiple parent models.

These methods are summarized below.

1. Comparison of the Modified Model to a Single Parent Model -

The analysis should include the following two elements:

- compression force divided by angle of contact per loop
- compression force after decay divided by angle of contact per loop

It should be performed at 10 mm if the lens is for capsular bag fixation only, 11 mm if the lens is for ciliary sulcus fixation only, and 10 and 11 mm if the lens is for either capsular bag or ciliary sulcus fixation.

The force range [upper force boundary (UFB) to lower force boundary (LFB)] associated with the parent model is determined from a series of equations in the standard which vary the number of standard deviations (s) used to determine the parent range from one to three as a function of the compression force. The force range for the modified IOL is always limited to ± one standard deviation. The other restrictions in the standard apply, for example:

- the modified IOLs compressed angle of contact (AC) should be within 40% of the value for the parent model;
- a modified model should be of the same loop type (open-loop or closed-loop);
- the maximum standard deviation is for the calculations is restricted to 20% of the mean force value at the compressed diameter(s), both initially and after decay.

For the modified lens to be considered a Level A modification of the parent model, some part of the range defined by the UFB/AC and LFB/AC for the parent model and modified model should overlap.

2. Comparison of the Modified Model to a Multiple Parent Models -

The analysis should include the following two elements:

- compression force as a function of angle of contact per loop
- compression force after decay as a function of angle of contact per loop

The other applicable restrictions associated with the comparison to a single parent model apply.

For each of the multiple parent models, the force values as a function of loop AC for each overall diameter and condition should be graphed.

For the modified lens to be considered a Level A modification of the parent models, some part of the force ranges for the modified model should fall within the boundary ranges defined by the force characteristics of any two parent models which are separated by not more than 30° of AC at each of the test conditions.

V. Sterility Testing

A. General

All testing should be performed on the finished product as marketed. The test methods specified below are suggested methods. Alternative sterilization and test methods are permitted if appropriately validated. The omission of certain tests should be justified with a valid scientific argument/rationale.

B. Validation of Sterilization Method

1. Steam Sterilization -

Validation of steam sterilization should be carried out in accordance with the requirements of ISO 11134.

2. Ethylene Oxide (EO) Sterilization -

Validation of EO sterilization should be carried out in accordance with the requirements of ISO 11135.

Sponsors may perform parametric release of EO-sterilized lenses by providing a validation which includes:

- the parametric release requirements specified in ISO 11135;
- documentation of the successful completion of end product sterility testing, pyrogen testing and EO residual testing on all lots produced over one calendar year
- documentation that each sterilization cycle that was run during the same calendar year met cycle specifications

  Note - For sponsors with sterilization and storage in stable climates (with little or no seasonal temperature or humidity variations), six months of the documentation described above is sufficient

3. Radiation Sterilization -

Validation of radiation sterilization should be carried out in accordance with the requirements of ISO 11137.

4. IOL Bacteriostasis/Fungistasis testing -

Bacteriostasis/fungistasis testing should be carried out in accordance with the requirements of USP 23, <71>, 1995).

5. Bacterial Endotoxins -

Bacterial endotoxin testing should be conducted in accordance with a validated bacterial endotoxin test that includes an inhibition/enhancement test (see: USP 23, <85>, 1995).

Acceptable bacterial endotoxin concentration levels are described in FDA Guideline: "Validation of Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for . . . Medical Devices," December 1987.

6. Package Integrity Testing -

Package integrity testing should be performed regardless of sterilization method and may consist of either of the following:

- a microbial barrier test in combination with a validated seal integrity test; or
- a validated whole package physical integrity test in combination with a validated seal integrity test.

Examples of physical integrity testing can be found in ISO 11607. References for microbial barrier testing can be found in the following articles, published in Medical Device & Diagnostic Industry (MDDI):

1. Placencia, Ana M. et al, "FDA Exposure Chamber Method," May, 1986.

2. Reich, Robert R., "A Method for Evaluating the Microbial Barrier Properties of Intact Packages," March, 1985.

3. Schneider, Philip M., "Microbial Evaluation of Package and Packaging Material Integrity," May, 1980.

C. Product Release Testing

1. Sterility -

Sterility testing should be conducted in accordance with a validated sterility test that includes a Growth Promotion Test (see USP 23, <71>, 1995).

2. Bacterial Endotoxins -

Bacterial endotoxin testing should be conducted in accordance with a validated bacterial endotoxin test (see: USP 23, <85>, 1995).

Acceptable bacterial endotoxin concentration levels are described in FDA Guideline: "Validation of Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for . . . Medical Devices," December 1987.

3. Ethylene Oxide Residual Testing

EO residual testing should be carried out in accordance with ISO 10993-7 (1995), with the following modifications:

- The procedure should consist of a solvent exhaustive extraction or a head space exhaustive extraction.

Note - Sponsors should choose a solvent that adequately swells or dissolves the lens material to facilitate extraction of the ethylene oxide molecules. A headspace method may be used if it has been validated to demonstrate that the extraction is as exhaustive as a solvent method. Alternatively, a sponsor may demonstrate the relative efficiency of an extraction method and adjust the internal release specifications accordingly.

- The ethylene chlorohydrin (ECH) residue in intraocular lenses (IOLs) should not exceed 2.0 µg ECH per lens per day, not to exceed 5.0 µg per lens.

  Note 1 - Ethylene glycol residues should be sufficiently controlled by the limits set for ethylene oxide and ethylene chlorohydrin residues.

  Note 2 - Initially, EO residual testing should be performed on every lot. However, sponsors may provide historical data to support a request for less frequent testing (e.g., quarterly, semiannually).

VI. Shelf Life and Shipping Testing

A. General

The test methods specified below are suggested methods. Alternative methods are permitted if appropriately validated. The omission of any tests should be justified with a valid scientific rationale.

A study protocol should be developed prior to initiation of the study.

The study should demonstrate that the parameters assessed with regard to safety and efficacy are within the original manufacturing specifications at the conclusion of the study. If a manufacturer wishes to maintain the possibility to resterilize finished IOL lots, the finished IOL lot(s) used in the stability study should have undergone the maximum number of sterilization cycles allowed under the manufacturer's procedures.

B. Materials and Methods

1. Test Samples -

The manufacturing lot(s) used for the stability study should be representative of normally produced manufacturing lots, and be packaged in the manner intended for marketing. A minimum of 10 lenses per test should be evaluated. Seal/closure integrity and microbial barrier testing may be performed on packages without an included IOL. However, microbial barrier testing should also include 10 negative controls and 1 positive control.

The number of IOL lots and the diopter range of the test samples should be in accordance with the provisions in Annex A.

Note 1 - In certain cases, more than one of the tests listed in Annex A may be performed on a single IOL (e.g., dioptric power, imaging quality and spectral transmission may all be measured on the same IOL), thereby reducing the total number of lenses needed.

Note 2 - When the manufacturing method does not allow different finished intraocular lens lots to be produced within a reasonable time, a subdivision of one finished intraocular lens lot into sub-lots may be employed in the studies. (Refer to the definition of "finished intraocular lens lots.")

2. Analytical Methods -

Suitable analytical methods should be chosen for the tests indicated in Annex A and for any additional tests contained in the study protocol. The methods selected should be recorded. If a method is selected that is not included among those listed in Annex B of ISO/DIS 11979-6 or those recommended in other parts of this guidance document, the method and the details of its validation, demonstrating the capability of the method, should also be documented.

C. Real-time Shelf-life Studies

For one of the finished intraocular lens lots, the tests chosen from Annex A should be carried out initially and at intervals in accordance with the protocol up to and including the manufacturer's desired expiration date. The other finished intraocular lens lots should be tested at least initially and at the desired expiration date.

The parameters measured should remain within the specified limits of the applicable parts of this guidance document. In case there are no limits specified in this guidance document, the parameters measured should remain within the manufacturer's internal finished product release specifications. If, during the course of the study, a parameter is found no longer to conform to the specifications at two or more time intervals, the maximum shelf-life of the intraocular lens under study has been reached at the last conforming measurement point.

1. Product Stability Studies -

Annex A lists tests that should be performed depending on lens type. For new lens types, additional parameters should be considered for testing, depending on the nature of the lens material. In case a specific test listed in Annex A has not been carried out, the justification for the omission should be provided.

Testing for changes due to interaction with the packaging material should be considered, as should testing for changes in the concentration of additives and coatings in addition to those listed in Annex A.

2. Package Integrity Studies -

As listed in Annex A, package integrity testing should consist of a validated seal integrity test in combination with microbial barrier test or a validated whole package physical integrity test. Examples of methods for physical integrity testing, some of which may have been previously validated, can be found in ISO 11607.

D. Accelerated Shelf-life Studies

Studies performed under accelerated conditions are likely to speed up any degradation processes, and therefore permit extrapolation of intervals under accelerated conditions to intervals at normal storage conditions. For microbial barrier testing, the accelerated conditions should involve storage at a specified temperature and with a relative humidity of at least 40%. If a sponsor wishes to perform sterility testing in lieu of microbial barrier testing, the storage temperature should be no higher than 45°C. The corresponding real-time shelf-life is calculated by multiplying the studied time period by $1.8^{(Ta - To)/10}$, where T_a is the accelerated temperature and T_O is the typical storage temperature (usually room temperature).

Accelerated studies should be carried out in the same way as real-time studies with the exception of the conditions chosen. It is important that lenses to be measured be allowed to equilibrate to the same conditions as at the initial measurements before being tested.

> Note - IOLs which have been aged under real-time conditions may be aged further under accelerated conditions. The established shelf-life would be the length of the real-time testing plus the real-time equivalent of the accelerated testing.

FDA prefers that real-time testing be performed for establishing shelf life; however, we have historically accepted up to 5 years of accelerated testing without corresponding real-time testing for PMMA and cross-linked polydimethylsiloxane IOLs which are packaged in Tyvek pouches. A scientific rationale should be provided to establish a shelf-life beyond 5 years through accelerated testing without corresponding real-time data.

For new materials, real-time testing should be performed.

> Note - Sponsors may submit a rationale to support accelerated testing (without corresponding real-time testing) for materials other than PMMA or cross-linked polydimethylsiloxane. The rationale should demonstrate that the material has a history of use in IOLs that have been produced by more than one manufacturer.

E. Shipping Tests

In view of the temperature fluctuations that can occur during shipment, the manufacturer should consider the maximum and minimum temperatures which the IOL is designed to withstand. The manufacturer should obtain data and records to demonstrate that the IOL remains within its specifications having been exposed to the maximum temperature for 24 hours and similarly, after having been exposed to the minimum temperature for 24 hours. Alternatively, the manufacturer should study the lenses at the temperatures and durations described in ASTM D-4169-94.

The tests that should be performed in the shipping studies are listed in Annex A. The drop and vibration testing listed in Annex A should be performed according to the methods described in ISO 2248 and ISO 8318. Both the package and the product should be inspected following these tests and the packaged product should be considered to have satisfactorily passed the test if, upon examination, the product is free from damage and the container still affords functional protection to the content.

VII. Clinical Investigation

A. General

The general requirements described in 21 CFR Part 812 apply to the clinical investigations of IOLs.

The following also should be considered in the planning of any clinical study of IOLs:

1. In the case of IOLs designed for either the posterior or anterior chamber, a separate clinical investigation should be performed to assess the clinical performance of the IOL in each chamber.

2. Data from the study may be submitted prior to the completion of the study, when the number of subjects required for the study has reached the final form. Subsequent reports should include the clinical results for any other subjects enrolled in the study who were not available at the time of submission.

3. The clinical study should include only one IOL model, or that model and models which are Level A minor modifications of that model as described in FDA's draft IOL guidance document (Section IX). Be advised that if multiple models are included in one study, only those models with at least 100 subjects will be considered parent models for future modifications.

4. Generally, bilateral implantation will not be allowed during the first phase of the study. Protocol waivers requesting bilateral implantation for individual subjects enrolled in the first phase of the investigation will be reviewed on a case-by-case basis. Bilateral implantation may or may not be approved for the second phase of the study. The protocol should define the criteria for bilateral implantation in the second phase of the study.

   Although the second eye should not be included in the study population, the second eye should be followed to the final case report form. The data from these subjects' second eyes should be analyzed separately and included in the premarket submission or final report/notice of completion of the PDP.

5. The investigational IOL may be compared to either historical controls or a concurrent control population. If a concurrent control population is used, the sample sizes should be sufficient to detect differences in adverse event and visual acuity rates between the test and control populations which are equivalent to the detection limits derived from the study described below which uses an historical control population.

6. The clinical study described below is for investigations of monofocal posterior and anterior chamber IOLs for the correction of aphakia. Any additional claims may require modifications in sample size, endpoints, etc.

B. Elements of the IOL Clinical Protocol

The following are elements of a clinical protocol which may be used by the sponsor to collect sufficient, relevant and appropriate data to determine the safety and effectiveness of anterior and posterior chamber monofocal IOLs for the correction of aphakia. These elements are described in greater detail in ISO/DIS 11979-7. The elements below include minor modifications of some of the elements of this ISO/DIS:

1. Control population -

   An historical or concurrently run control population (an appropriate FDA-approved IOL) may be used. In the past, the data reported in Stark, W. J., et al., *The FDA Report on Intraocular Lenses,* Ophthalmology, 90(4):311-317, 1983 has been used as an historical control. These data have been updated from recent, PMA approved IOL experience (Annex B). If a sponsor chooses to use an historical control population, the data in Annex B may be used as the historical control.

2. Sample size -

   A minimum of 300 subjects should be used when the IOL is compared to the historical control population for the purpose of determining the investigational IOL's safety and effectiveness.

   An IOL which is a Level B modification of a parent IOL should have a minimum sample size of 100 subjects when the IOL is compared to the historical control population for the purpose of determining the investigational IOL's safety and effectiveness.

   The maximum subjects enrolled in any study should be limited to no more than 143% of the sample size that the sponsor intends for the study.

   After all the subjects needed for a study have been enrolled, a sponsor may request approval to enroll additional subjects into a modified core study of the lens so that investigators may continue their experience with the lens until any premarket approval is obtained.

3. Number of investigators -

   Each investigator should contribute a minimum of 20 subjects to the study population, but not more than 25% of the subjects in the study.

4. Lost to follow-up subjects -

   The lost to follow-up subjects should be less than 10% for one year studies and less than 30% for three year studies. These rates are based on FDA's experience with IOL studies of these durations in elderly subjects.

5. Study duration -

   One year for all posterior chamber lenses.

Three years for all anterior chamber IOLs. The data from these IOLs may be submitted for approval at one year in all cases except for the case of closed loop anterior chamber IOLs which should be followed three years prior to approval. The IOLs which are submitted for approval based on the one year data are routinely followed for the additional two years of the three year study as a condition of approval of the PMA. The three year data should be provided in a report to FDA.

If the sample size at case report form 7 of a three year study is less than 300, a sponsor may make up the missing subjects from any modified core study population.

For a Level B study, the study duration is to Form 4.

6. Study phases -

The first phase of the 300 subject study should consist of no more than 100 subjects. When all 100 have been enrolled and 50 have reached Form 4, the data should be submitted to FDA and if acceptable the second phase of the investigation may begin and include the remainder of the population. A Level B study generally will not require phases.

7. Reporting periods and sample case report forms -

The one-year clinical investigations should include all the case report forms listed below.

Case Report Form 0: Pre-operative/Operative reporting
Case Report Form 1: Post-operative reporting 1 or 2 days post-operatively
Case Report Form 2: Post-operative reporting 7 - 14 days post-operatively
Case Report Form 3: Post-operative reporting 30 - 60 days post-operatively
Case Report Form 4: Post-operative reporting 120 - 180 days post-operatively
Case Report Form 5: Post-operative reporting 330 - 420 days post-operatively

The three-year clinical investigations should include all the case report forms listed above and both case report forms defined below:

Case Report Form 6: Post-operative reporting 630 - 780 days post-operatively
Case Report Form 7: Post-operative reporting 990 - 1140 days post-operatively

The Level B study of a modified IOL should include all case report forms up to and including Form 4.

Unscheduled visits and the procedures to capture adverse events that may occur between case report forms should be addressed in the clinical investigational plan.

The minimum number of case report forms at each reporting period should be equivalent to at least the minimum sample size for the study, but all data from all visits must be reported to FDA.

Samples of case report forms are provided in ISO/DIS 11979-7 Annex A. Additionally, data on wound size and placement (e.g., clear corneal, limbal, etc.) should be collected.

8. Adverse Events -

The clinical report forms should include forced-choice listings of whether the following adverse events are present. The adverse events are grouped either as cumulative or persistent adverse events, depending upon the way in which they will be analyzed. Additionally, the forms should allow for the recording of other adverse events.

Cumulative Adverse Event: The total number of adverse events which have occurred at any time during the investigation.

Persistent Adverse Event: An adverse event which is present at the one year postoperative visit.

> Note: when reporting data from 3-year studies, any adverse events present at 3 years shall be reported as persistent at 3 years.

CUMULATIVE ADVERSE EVENTS:

Endophthalmitis: Inflammation of tissues inside the eyeball. Can be confirmed intraocular infection or sterile.

Hyphema: Blood in the anterior chamber, present over a period of time.

Hypopyon: Accumulation of white blood cells in the anterior chamber.

Lens Dislocation: Displacement of the lens from its intended place.

Macular Edema: Swelling of macular tissue from excess fluid accumulation. Note: Macular edema is to be reported both as a cumulative and as a persistent adverse event.

Pupillary Block: Blockage of aqueous flow through the pupil, from the posterior chamber into the anterior chamber, caused by tight contact between the pupillary margin of the iris and the lens (or vitreous face only if aphakic, unless the IOL slips into the vitreous).

Retinal Detachment: Separation of retina from the underlying pigment epithelium associated with retinal hole formation (rhegmatogenous).

Secondary Surgical Intervention: Any secondary surgical procedure that can reasonably be expected to be IOL-related.

Exclude:
Retinal Detachment Repair
Posterior Capsulotomy

Include:

Iridectomy for Pupillary Block
Vitreous Aspiration for Pupillary Block
Repositioning of Lens
IOL Removal for Inflammation
IOL Replacement
Other

PERSISTENT ADVERSE EVENTS:

Corneal Edema: Fluid in stromal layer of cornea ± epithelial edema (bullae or microbullae).

Iritis: Inflammation of the iris, causing pain, tearing, blurred vision, small pupil (miosis), and a red congested eye. Evidenced by flare and/or cell in the anterior chamber with or without keratic precipitates.

Macular Edema: See definition under "cumulative adverse events."

Raised IOP Requiring Treatment : Persistent elevation of intraocular pressure requiring medical and/or surgical treatment.

9. Modified Core -

Modified core studies will continue to be allowed after the enrollment of the initial study population. The sponsor may request approval for modified core studies after the enrollment of all core subjects for premarket approval purposes. For a parent model group (i.e., a 300 subject study population), the modified core implant limit is 2200 lenses. For a Level B model group (i.e., a 100 subject study population), the modified core limit is 1600 lenses.

Modified core studies will include mandatory reporting of adverse events and modified core data must be reported in PMA updates required by the PMA regulation, 21 CFR Part 814. The following forms are needed for a modified core study:

preoperative/operative case report form
case report form 4
case report form 5 (not required for Level B studies)

For three-year studies, sponsors should collect case report form 6 and 7 for their modified core subjects. Form 7 data from the modified core population may be needed in order to obtain 300 subjects.

C. Data Analyses

1. Accountability table -

An accountability table as described below should be provided at the time of the submission of the final data analysis to FDA. For a three-year study, this table should

also be provided with the three-year data analysis.

Total Subjects: _____

Total subjects at each form:

Form 1 _____
Form 2 _____
Form 3 _____
Form 4 _____
Form 5 _____
Form 6 _____
Form 7 _____

Missing subjects (at final form):

Lens replacements _____
Deceased subjects _____
Missing Form 5, but seen at a later visit _____
Not seen, but status obtained (e.g., by telephone) _____
Lost to follow-up _____

Active subjects (not reached final form prior to accountability analysis) _____

2. Data analysis tables -

The adverse event and Best Corrected Visual Acuity (BCVA) rates should be compared to the IOL historical control population provided in Annex B.

The clinical data should be analyzed in terms of the following, at a minimum, to look for trends which may suggest a problem with the lens design which may not be apparent from an overall analysis of the adverse event and visual acuity (VA) rates. This clinical data evaluation should provide insight into whether an IOL's failure to meet the clinical performance levels associated with the historical or concurrent control populations is device related.

- VA by age

  Note - VA should be analyzed down to 20/20 in all analyses.

- best-case VA
- VA by adverse event
- VA by pre-operative ocular pathology
- rates of cumulative and persistent adverse events
- rates of cumulative adverse events by age
- rates of persistent adverse events by age
- rates of other adverse events
- VA by investigator
- adverse event by investigator
- patient-by-patient analysis of reasons why patient failed to achieve 20/40 VA

- posterior capsulotomy rate by form
- compilation and analysis of wound size and placement
- demographic analysis

  Note - Best-case visual acuity and rates of cumulative and persistent adverse events should be analyzed in terms of demographic variables (e.g., gender, race) to determine if bias exists in the study. Additional analysis, such as by iris color, may be needed in the future.

- lost-to-follow-up analysis

  Note - The effects of patients lost to follow-up should be explored as comprehensively as possible. If methods other than extrapolating the results of a lost to follow-up subject's clinical results to the final form needed for the study are used (last visit carried forward), detailed explanations of the procedures employed for dealing with missing data (i.e., data imputation methods) should be described and the potential implications of such analyses on the overall study outcomes provided.

3. Outcomes criteria

   The clinical data will be compared to either the historical or a concurrently-enrolled control population (an appropriate FDA-approved IOL). If the safety and effectiveness of the test population in terms of adverse events and visual acuity is not statistically significantly worse than the control population, the test IOL will have performed successfully. See ISO/DIS 11979-7, Annex B for statistical methods.

VIII. Labeling

The purpose of this section of the guidance is to update existing intraocular lens (IOL) labeling so that it conforms to the Office of Device Evaluation labeling guidances and represents present medical standards of ophthalmic practice. This section was developed with clinical input from FDA's Ophthalmic Devices advisory panel. A sample package insert is included in Annex C. This annex contains an example of a package insert with the labeling information needed for all IOLs and other specific lens types. A generic package insert may be used by the sponsor for a series of lens models, with the lens specific information contained on the packaging.

A "label" is defined as a display of written, printed or graphic matter upon the immediate container of any article. For medical devices, the packaging and the package insert are the major components of the labeling.

The sale, distribution and use of IOLs are restricted; therefore, the label must include the caution restricting the device to sale by or on the order of a physician. In accordance with the provisions of section 502(r) of the Federal Food, Drug, and Cosmetic Act (the act), advertisements and other descriptive printed material issued by the manufacturer, packer or distributor with respect to a restricted device must include, but is not limited to, the following:

1. a true statement of the device's established name (common or usual name unless there is an official name designated by FDA or recognized in an official compendium), printed prominently and in type at least half as large as that for any trade or brand name for the device; and

2. a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications.

References: Office of Device Evaluation (ODE), Device Labeling Guidance, General Program Memorandum #G91-1

Code of Federal Regulations, 21, Chapter 1, Subchapter A, Part 1, Subpart B

ODE, Medical Device Labeling - Suggested Format and Content, Draft Guidance (available at http://www.fda.gov/cdrh/ode/labeling.html)

Device Description

In this section, the labeling should include a brief description of the device, how it functions and its significant physical characteristics. The trade and generic names for the IOL should be included and the lens should be identified as ultraviolet-absorbing (if applicable) and for posterior or anterior chamber implantation.

Indications

The "indications for use" identify the target population of the device for which there is valid scientific evidence demonstrating the device's safety and effectiveness. The most general population indicated for IOLs includes individuals requiring the visual correction of aphakia. Additional information should be described in the indications to identify the subgroups of this "most general" population that were studied in the clinical trial. For instance, to date, IOLs have been indicated only for adults over 60. As discussed at previous Panel meetings, FDA is working on guidance that would allow all IOLs to be implanted in adult subjects rather than just in persons 60 years of age and older. Once guidance on this lower age indication (to 18 years of age and older) is available, we anticipate IOL indications to read: "The [....] IOL is generally indicated in the visual correction of aphakia in adults in whom a cataractous lens has been removed." The intended placement will vary depending upon the lens.

Contraindications

Contraindications include situations in which the device should not be used because the risk of use outweighs any possible benefit. Known (studied) hazards should be listed. For instance, a coating on an IOL may be contraindicated for individuals known to be allergic to a component of the coating.

Warnings

FDA labeling guidelines state that the "Warnings" section should describe serious adverse events and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur.

The labeling should include an appropriate warning if there is reasonable evidence of an association of a serious hazard with the use of the device. A causal relationship need not have been proved.

A warning is appropriate when the device is commonly used for a disease or condition for which there is a lack of valid scientific evidence of effectiveness for that disease for condition and such usage is associated with a serious risk or hazard.

The sample insert in Annex C lists the current IOL warnings as recommended by FDA's Ophthalmic Devices advisory panel.

Precautions

The "Precautions" section describes any special care that is to be exercised by the practitioner for the safe and effective use of the device. The sponsor should identify information to avoid certain risks in connection with implantation of the device, and information regarding the risks of reciprocal interference posed by the presence of the device during specific treatment. Precautions to be taken in the event of changes in the performance of the device that may be specific to the device should be described. Special patient populations that might be at risk or associated with a specific hazard should be identified in this section, as well as precautionary statements not appropriate for inclusion under other sections of the labeling.

The sample insert in Annex C lists the current IOL precautions as recommended by FDA's Ophthalmic Devices advisory panel. Specifically, the Panel advises the physician to weigh the risk/benefit ratio under various circumstances before implanting an IOL.

Adverse Events

An adverse event is defined as an predicted or unpredicted undesirable effect reasonably associated with the use of the device. For IOLs, this section would include complications associated with the surgical implantation. This section should include all adverse events and directions to the other sections of the labeling for additional information regarding these adverse events. Adverse events experienced during the study of the device listed in descending order of frequency should be included in this section.

Clinical Trial

The "Clinical Trial" section is used by an implanting physician to determine the risk/benefit ratio, reliability and performance standards of the lens. Information on the race and gender of the study population should be included.

This section should include the best case visual acuity along with FDA grid results for comparison. Sponsors should also include tables showing cumulative and persistent sight threatening complications for the study population, and adverse events for the total study and modified core populations. Under the adverse event subsection, secondary surgical interventions should be delineated by reason with the appropriate rate of occurrence listed by reason. In addition, the sponsor should include the number of implants as of a certain date, and the overall incidence of reported adverse events.

Detailed Device Description

Package Insert:
The insert for IOL labeling should contain a description of the properties of both the optic and loop of the IOLs, including the placement of the IOLs.

The IOL characteristics for the insert should be consistent with the information described in the labeling (package insert) example provided in Annex C.

Outside Box:
In addition to the package insert, the outside of the IOL box should contain a detailed description of the IOLs. FDA requires that the following descriptive information be contained on the box: manufacturer name and address, trade name of the lens, model number, lot/serial number, expiration date, power in diopters, a lens constant (see information in the "Lens Power Calculations" below), overall diameter, body diameter, UV or non-UV, anterior or posterior chamber, and optic and loop materials. A diagram showing a front view of the lens configuration (depicting loop configuration, optic shape, and other, including positioning holes, ridges, eyelets, etc.) should be included so that right-handed and left-handed lenses can be clearly distinguished. A side view diagram of the lens, with anterior and posterior sides marked and the optic configuration depicted, should be included.

Lens Container and/or Pouch:
FDA recommends that the inside lens container and/or the pouch also include the manufacturer name, trade name of the lens, model number, lot/serial number, power in diopters, and the statements "STERILE", "Do not reuse," and "Do not resterilize." The label should state "left-handed lens" if applicable.

Directions for Use

This section should provide directions under which the practitioner can use the device safely and for the purpose for which it is intended. Details of any further treatment or handling needed before the device can be used should be included in this section.

Lens Power Calculations

Background

The IOL power needed for a specific patient depends upon the optical axial length of the eye, the optical power of the cornea, and the position of the IOL within the eye and the desired post-operative refraction. Surgeons have a variety of formulae at their disposal for calculating the desired implant power. These formulae typically handle the implant position through use of a constant, referred to in this document as the lens power constant. "A-constants", "ACD's", and/or "Surgeon Factors" are examples of the most commonly used lens power constants.

In the past, IOL manufacturers have voluntarily provided one or more lens power constants on the outer box or through catalogs. However, the standards of care have improved over the years to the point that the availability of lens constants is considered essential. This guidance describes information expected to be developed by sponsors relating to lens power constants for new lens models.

Portions of this guidance may be applicable to efforts by FDA to make lens power constant information widely available for nearly all IOL models. This effort is being done in partnership with industry and surgeons under the auspices of ANSI Z80.7 and ophthalmic professional societies. The intent of this effort is to assure that lens constant data are available in a format that can be updated. The outcome of this partnership of public and private interests will likely influence the sponsor's choice of how to publish lens constant data for new lens models.

The basic premise of any of these lens power constants is that two IOLs of the same median power (about 22 D) and the same lens constant would be expected to create the same refractive state once implanted. This condition is effectively met if the second principal planes of both IOLs are in the same location. Differences in lens shape or material may cause the actual surfaces to be in different locations. However, if the second principal planes are in a fixed position, the difference in the final refractive state created by two different designs of the same power will be too small to detect. Therefore all lens power constants are, in some sense, descriptions of the position of the IOL's second principal plane (PP).

For a variety of reasons, currently available lens power constants lack sufficient consistency that the above description of equivalence is assured. With a given surgical procedure, differences in measuring technique and equipment create large systematic discrepancies between sites. These systematic differences affect the sponsors' determination of the supplied lens power constants. Although a sponsor can determine a mean power constant with statistical confidence, these systematic discrepancies affect the direct application of the lens power constants to any particular setting or facility. Authors of the different formulas recommend "personalization" of the power constant to reduce the systematic errors. This FDA guidance is intended to minimize the variation of these biases from sponsor to sponsor, at least for new lens models. However, it does not remove the need for such personalization.

Each of the current lens power constants is defined in the context of the particular power calculation formula. FDA does not find it appropriate to recommend any particular power formula as that constitutes a de facto standard that may limit the ability of this technology to evolve. The literature does provide conversion information to the most commonly used formulae (ref. a). The authors of these formulae and other scientists may be able to improve the conversions provided.

Implementation

For lenses that are undergoing a clinical investigation, the sponsor should use whatever method they believe provides the best estimate for an initial "theoretical lens power constant" that will be used by the investigators in their clinical study.

For future marketing submissions, FDA proposes that a "clinical lens power constant" based on clinical data be submitted to FDA for those lenses which would typically require a clinical study prior to marketing (e.g., those submitted in an original PMA/PDP or as a "Level B" model). The refractive outcomes from the investigational subjects should be analyzed to determine if error exists in the initial "theoretical lens power constant" that was used throughout the investigation (see Reference b). If, for a "Level B" model, the clinical data are not sufficient to meet statistical requirements (see section below on the determination of a lens power constant by clinical evaluation), the "clinical lens power constant" should be used only after the statistical requirements are reached. If supporting data are obtained to meet the statistical requirements, the sponsor should submit the "clinical lens power constant" in the next annual report to the PMA or PDP.

New IOLs that are Level A modifications of those lenses for which clinical data were evaluated to validate the "clinical lens power constant" may use the "clinical lens power constant" from the clinical parent provided the modifications incorporated into the "Level A" model have no effect on lens second PP position. For "Level A" models for which the modifications could affect the lens second PP position, a "theoretical lens power constant" derived from engineering and clinical knowledge may be used provided there is a distinction that the lens power constant was determined theoretically rather than through clinical data.

After PMA approval or PDP completion, if the results of additional clinical testing results in a necessary change to the "clinical lens power constant," FDA should be notified of the modification of the constant and provided the supporting data in the next annual report to the PMA or PDP. Also, a manufacturer may use post-approval clinical data to validate a "clinical lens power constant" for lenses approved prior to the release of this guidance and for other lens models for which the lens power constant was determined theoretically. The notification of the change and the data supporting the "clinical lens power constant" should be submitted in the next PMA/PDP report.

FDA has worked through ANSI to provide a mechanism for publication of lens power constants (theoretical and clinical) in the Journal of Cataract and Refractive Surgery. These will be published in the January issue beginning in 1999. Jack Holladay, M.D. (holladay@houstoneye.com) has agreed to coordinate this activity, and companies that want to participate should provide information on the latest theoretical and clinical power constants for their lenses to Dr. Holladay by October 15 of each year to be included in the next January issue. Companies that decide not to make the power constants for their lenses available in this journal article should provide the power constants in their labeling.

If a sponsor chooses to place their lens power constant in their labeling, their choice for lens power constant (e.g., A-constant, ACD, SF, ELP, etc.) should be put on the outer box. In any labeling, power constants should be asterisked and include a footnote specifying the basis of the power constant (either theoretical or clinical data). The month and year that the theoretical or clinical lens power constant was first included in the labeling should be added in parenthesis after the power constant.

Determination of a lens power constant by clinical evaluation

If regulatory approval for marketing requires a clinical evaluation, refractive data from that clinical evaluation should be used to determine a lens power constant.

To reduce bias due to surgical technique, unusual eyes and differences in equipment (A-scans, etc.), a manufacturer should obtain clinical data from a sufficient number of cases such that the standard error of the mean ($\sigma/n^{1/2}$) in the lens power constant is less than **±0.10 mm (approximately ± 0.2D).** A minimum of 10 surgeons with 20 to 30 cases each should be adequate to achieve this tolerance. Each included subject should have a postoperative visual acuity better than 20/40 to avoid inaccuracies in refraction.

"Level A" modifications with no effect on lens position

Modifications to lenses that do not affect the position of the second PP of the lens optic should have no affect on the lens power constant. The following "Level A" modifications are not believed to have an affect on the final lens second PP position:

- Mirror-image version of a model.
- Changes in loop features, such as the addition of notches, or the addition of small loops or rounded ends to loops.
- Additions, deletions, or moving of positioning holes.

Conversion from the manufacturer's choice of lens power constant to other constants

A physician can convert any lens power constant to the constant of the formula he prefers by applying conversion algorithms (see Reference a). It should be understood that two different IOL designs with the same power and lens power constant should be interchangeable in terms of resulting in approximately the same postoperative refraction in typical eyes (i.e., eyes requiring mid-range IOL powers), but may not be interchangeable in terms of postoperative refractive result in unusual eyes requiring IOL powers outside to the mid-range powers.

Physicians are encouraged to continue "personalizing" all lens constants to enhance their accuracy in prediction of postoperative refraction with their personal technique and equipment. Calculation of powers for back-up lenses should always be performed prior to surgery, so that these can be available at the time of surgery.

References

a) Holladay JT. Standardizing constants for ultrasonic biometry, keratometry, and intraocular lens power calculations. J Cataract Refract Surg 1997; 23:1356-1370.
b) Holladay JT, Maverick KJ. Relationship of the actual thick intraocular lens optic to the thin lens equivalent. Am J Ophthalmol 1998;126,3:339-346.

Lens Specific Requirements

Soft Optic Material IOLs

Separate listings for ECCE and phacoemulsification are not routinely necessary for soft material IOLs.

Under the "Directions for Use" section, the sponsor should provide instructions for the implanting surgeon on the type of folders/injector systems to be used for the packaged lens. FDA has approved specific folders/injector systems for different intraocular lens models. The labeling should list those folders/injector systems that have been validated to be used with the lenses. Additionally, the sponsor may state that other approved folders may be used with the lens, a listing of which should be made available from the sponsor upon request.

UV/Non-UV Absorbing Lenses

For UV-absorbing lenses, the sponsor should include the UV transmittance curve with the 10% transmittance cutoff wavelength for a 20 diopter lens or the highest and lowest power lenses. Non-UV-absorbing lens labeling should contain the statement "This lens does not significantly absorb ultraviolet-light in the range of 320-400 nm."

Anterior Chamber Lenses
For anterior chamber lenses, the sponsor should include the sizing information, the mechanical testing data, and additional warnings. Clinical data should be broken out by type of surgery as warranted.

Surface Modified Lenses
For surface modified lenses, FDA may require additional data in labeling to support any implied or stated claims.

Small Optic (< 5.5 mm)
Lenses with a small optic require an additional warning regarding the risks associated with decentration of lenses with a small optic.

Lenses manufactured with CFCs and other ozone depleting materials
These lenses should have an additional statement which can be found in the February 11, 1993 and June 29, 1993 Federal Registers (58 FR 8136 and 34812, respectively).

High (>34 D) and Low (<4 D) IOLs
Labeling for these lenses should include the following additional warnings:

Warning
This lens is not intended, nor should it be used, for a clear lens exchange.

Special consideration should be given to the dimensions of lenses at the extreme ends of the power range in relation to the anatomical clearances in the patient's eye. The potential impact of factors such as optic central thickness, optic edge thickness, and overall lens size on the patient's long-term clinical outcome should be carefully weighed against the potential benefit associated with the implantation of an intraocular lens. This is particularly true for anterior chamber lenses. The patient's clinical progress should be carefully monitored.

IX. Modifications

A. General

The tables that follow address changes that commonly occur during the clinical study and/or after PMA approval or completion of a PDP. Those changes that require prior approval from FDA must be submitted in an IDE or PMA supplement, as appropriate, or be included in the approved PDP protocol. Those changes that do not require previous FDA approval may be submitted in the periodic reports. As noted, some changes may be implemented without prior FDA approval, for instance, if validated with recommended tests or in certain cases. The tests listed for each modification are recommended tests only and may be waived with a scientific rationale. The term "mechanical testing" refers to the tests described in Section IV of this document.

B. Device Design Changes

Two levels of modifications have historically been associated with a parent (i.e., a clinically studied) IOL: Level A and Level B.

Level A

Level A modifications of a parent model do not require a clinical study. If the modified model poses additional clinical questions which cannot be adequately addressed by preclinical testing, such as potential tissue damage associated with a modification in implantation technique necessitated by the modified design, the lens no longer qualifies as a Level A modification and will require at least a 100 subject clinical study.

Level B

Level B modifications of a parent lens require a 100 subject confirmatory clinical study in addition to preclinical testing.

A Level B modification of a parent lens may be considered a parent lens for subsequent modifications if at least 100 subjects are implanted with the modified lens and completely followed, the lens meets all the specifications of the other parts of this guidance document, and the results of a clinical analysis indicate that there is no significant difference between its clinical performance and the historical control. The recommended clinical protocol is discussed in Section VII of this guidance document.

Note - The applicability column (first column) indicates the type of IOL for which the modification is appropriate:

P designates PMMA posterior chamber IOLs
A designates PMMA anterior chamber IOLs
SS designates posterior chamber IOLs with optics made from soft materials and loops made from standard materials (PMMA and PMMA monofilament, polypropylene, polyimide)
SN designates posterior chamber IOLs with optics made from soft materials and loops made from non-standard materials

SP designates posterior chamber IOLs made from soft materials with a plate design (i.e., no loops)

Except where noted, most changes to an anterior chamber IOL require a full clinical study. Sponsors may wish to contact FDA for further guidance on specific changes.

IOL Type		Modification and Recommended Testing	Prior Approval Required? Yes	No
		LEVEL A MODIFICATIONS		
P/SS/SN/ SP/A	1.	Mirror-image version of a model		X
P/SS/SN/ A	2.	Changes in loop features, such as the addition of notches, or the addition of small loops or rounded ends to loops. • The addition or deletion of a notch should be qualified through mechanical testing performed as described in Section IV of this document. • Other loop features do not require preclinical testing.		X
P/SS/SN	3.	Change in loop angulation from planar to a design with the body angulated posterior to the loops, which results in an increase in the sagitta value up to a maximum of 1.6 mm for the 20 D version (approximately 10° angulation) of the model. For lenses with loops of non-standard materials, measurement of forces in the z-direction is also required to demonstrate that the change in the loop has not significantly altered the expected placement of the lens in the eye from that which was studied clinically.	X	X
P/SS/SN	4.	Change in loop configuration, thickness, caliber or overall diameter. To determine if these changes result in modified lenses which are Level A modifications of the parent lenses requires an analysis of the change in mechanical properties that has occurred as a result of the modification. Two methods of comparing the mechanical properties of a parent model and a modified model are described in Section IV of this document. A sponsor may use either method. For comparisons between a modified model and a single parent model, the sponsor should demonstrate that the mechanical properties of the modified lens are not significantly different from the mechanical properties of the parent model. A detailed description with examples showing how to apply this method may be found in ISO/FDIS 11979-3. A recommended format for submission of this analysis in a periodic report can be found in Annex D of this document.		X

IOL Type		Modification and Recommended Testing	Prior Approval Required?	
			Yes	No
		For comparisons between a modified model and multiple parent models, the sponsor should demonstrate that the mechanical properties of the modified lens are not significantly different from the range of characteristics defined by the parent models. A detailed description with examples showing how to apply this method may be found in ISO/FDIS 11979-3. A recommended format for submission of this analysis in a periodic report can be found in Annex D. If a sponsor finds that a model is not a Level A modification with one method, an evaluation using the other method should be performed. If the modified lens does not qualify as a Level A modification with either method, the change becomes a Level B modification requiring a clinical study (see below). For lenses with loops of non-standard materials, measurement of forces in the z-direction is also required to demonstrate that the change in the loop has not significantly altered the expected placement of the lens in the eye from that which was studied clinically.	X	
P/SS/SN/ SP	5.	Change in optic size and addition of tabs to the periphery of the body. Changes in optic circumference design are allowed if the length is not less than 5.0 mm along any meridian (e.g., going from a circular to an ovoid body), and not greater than 7.5 mm along any meridian.		X
P/SS/SN/ SP/A	6.	Additions, deletions, or moving of positioning holes. Positioning holes, or any other obstruction that interferes with the performance of the optic, should be placed no less than 2.125 mm from the center of the optic to minimize the possibility of glare of other visual disturbances that may result from these structures.		X
P/SS/SN/ SP/A	7.	Change in the dioptric power range within the +4 to +34 D range.		X
		Change in the dioptric power range outside the +4 to +34 D range, when the sponsor does not have previous approval for other models in the same power range.	X	
		Change in the dioptric power range outside the +4 to +34 D range, when the sponsor has previous approval for another model(s) in the same power range. Additional validations should be performed as necessary (e.g., new optic shape factor). There is no limit to the power range that the sponsor may make available, provided each power within the available range meets the specifications described in Section III of this document.		X

IOL Type		Modification and Recommended Testing	Prior Approval Required? Yes	No
		Note - Sponsors should be advised that for certain combinations of optic shape factor and material, certain powers may not meet minimum optical quality levels because of the effects of spherical aberrations. In such cases, the powers made available should be restricted to those meeting the specifications of Section III of this document.		
P/SS/SN/ SP/A	8.	Change in optic shape factor. For posterior chamber lenses, the testing described in Section III of this document should be performed and if no new safety or effectiveness issues are raised by the testing, no FDA approval is necessary prior to implementation of the change.		X
		For anterior chamber lenses, the testing described in Section III of this document should be performed. Additionally, any change in the position of the anterior surface of the lens (relative to the base of the loops) that results from the new optic shape should be factored into the analysis requested in Section IV.D.3 for anterior chamber IOLs.	X	
A	9.	Change in overall diameter to add an additional size specific to patients with a certain anterior chamber width range.	X	
		LEVEL B MODIFICATIONS		
P/SS/SN	1.	Change in overall diameter that results in a lens modification that displays mechanical behavior that does not meet the requirements for a Level A modification as described above when compared to a single parent model or when compared to the range of acceptable mechanical behavior of parent models. The data from the evaluation of the mechanical behavior of the modified lens should be provided in addition to the results of the Level B study (including evaluation of forces in the z-direction, if applicable).	X	
P/SS/SN	2.	Change in loop configuration that results in a lens modification that displays mechanical behavior that does not meet the requirements for a Level A modification as described above when compared to a single parent model or when compared to the range of acceptable mechanical behavior of parent models. The data from the evaluation of the mechanical behavior of the modified lens should be provided in addition to the results of the Level B study (including evaluation of forces in the z-direction, if applicable). Note - If the change in loop configuration of the modified lens (e.g., a single-piece disc lens) appears to have the potential to cause different or greatly increased safety concerns as compared to the parent model(s), the new model should undergo the 300 subject clinical investigation required for new models.	X	

IOL Type		Modification and Recommended Testing	Prior Approval Required? Yes	No
P/*SS/SN*	3.	Change in loop caliber that results in a lens modification that displays mechanical behavior that does not meet the requirements for a Level A modification as described above when compared to a single parent model or when compared to the range of acceptable mechanical behavior of parent models. The data from the evaluation of the mechanical behavior of the modified lens should be provided in addition to the results of the Level B study (including evaluation of forces in the z-direction, if applicable).	X	
P/*SS/SN*	4.	Change in optic diameter outside the range from 5.0 mm to 7.5 mm. An evaluation of the mechanical behavior of the modified lens should be provided in addition to the results of the Level B study. Note - The sponsor should be aware that the evaluations of models that incorporate optics less than 5.0 mm in diameter should include clinical testing to evaluate the effects of glare on the subject's visual acuity that may result from the small optic.	X	
		OTHER		
P/S1/S3/A	1.	Any change that may affect safety and effectiveness and that is not addressed in this guidance or an approved PDP protocol.	X	

C. Material Changes

For any material or supplier change, the sponsor should discuss any manufacturing or quality control procedures that have been modified as a result of the change and demonstrate that the modified lens continues to meet previously established in-process and final release specifications.

The tests recommended below for material and supplier changes are suggested tests. A sponsor may request a waiver from tests in certain sections of this guidance document with a scientific rationale. Also, additional testing may be required if determined to be critical for FDA's evaluation of any potential impact of the change on safety and effectiveness.

Modification and Recommended Testing	Prior Approval Required? Yes	No
1. Change in loop or body material prior to completion of a PDP or completion of an IDE. To qualify a change in either loop or body material during the clinical investigation, the sponsor should ensure that at least 100 subjects are implanted with the modified lens and completely followed; the lens meets all the specifications of the other parts of this guidance document; and the results of a clinical analysis indicate that there is no significant difference between its clinical performance and the clinical performance of the parent lens.	X	

	Modification and Recommended Testing	Prior Approval Required? Yes	No
	• If a new body material in the same class (e.g., PMMA, cross-linked PDMS) and which requires similar manufacturing methods is chosen whose long-term safety can be supported by the ophthalmic literature, the modified lens should be investigated in a minimum of 100 subjects. • If a new body material is chosen that lacks long-term safety information, a full 300 subject investigation of lenses manufactured with the new material should be performed. • A new loop material should be investigated in a minimum of 100 subjects.		
2.	Change in loop material to another material that has been qualified by the sponsor by being a loop on part of a parent model, after completion of a PDP or approval of a PMA. This change should be qualified through an analysis of the mechanical behavior as described above for Level A modifications. If no new safety and effectiveness issues are raised by the testing, FDA approval prior to implementation is not necessary.		X
	If the modified lens does not meet the requirements for a Level A modification when compared to a single parent model or when compared to the range of acceptable mechanical behavior of parent models, then a Level B clinical study is required.	X	
3.	Change to a new loop material after completion of a PDP or approval of a PMA. If the change is to a new loop material, the testing from the following sections of this guidance document should be performed and all test results should be submitted: • mechanical • biocompatibility • shelf life and shipping (specifically, product stability); and • clinical (Level B study). Note - Certain biocompatibility testing may be waived with a scientific rationale.	X	
4.	Change to a new body material after completion of a PDP or approval of a PMA. If the change is to a body material which is new for the sponsor, and is a material whose long-term safety as a body material can be supported by the ophthalmic literature, the testing from the following sections of this guidance document should be performed and submitted: • mechanical; • optical • biocompatibility; • shelf life and shipping (specifically, product stability)	X	

	Modification and Recommended Testing	Prior Approval Required? Yes	No
	• sterility (if the lens is sterilized by ethylene oxide, residuals and aeration times should be requalified); and • clinical (Level B study). Note 1 - The literature articles must provide the identity of the material used and the sponsor must be using the identical material. Note 2 - Certain biocompatibility testing may be waived with a scientific rationale. If the change is to a body material which is new for the sponsor and whose long-term safety cannot be supported by the ophthalmic literature, a full 300 subject clinical study should be performed in addition to the testing above.		
5.	Change in supplier for a loop material (after completion of a PDP or approval of a PMA). If a sponsor can demonstrate that the loop material from the new supplier is chemically identical to the material from the present supplier with similar types and quantities of extractables from an exhaustive extraction, testing from the following sections of this guidance document should be performed and submitted: • mechanical; and • biocompatibility Note - Cytotoxicity is the only necessary toxicity test if the long-term safety of the material from the new supplier as loop material can be supported by the ophthalmic literature. This testing should be performed even if the new material has been shown to be chemically equivalent to the material from the present supplier. If the mechanical behavior of the new material qualifies as a Level A modification, prior approval from FDA is not necessary.		X
	If the mechanical behavior of the new material fails to qualify as a Level A modification, a Level B clinical study should be performed and prior FDA approval is required.	X	
	If the material from the new supplier cannot be demonstrated to be chemically identical, then the testing recommended for changes in loop material (see above) should be performed and the results submitted to FDA and approval obtained prior to implementation.	X	

	Modification and Recommended Testing	Prior Approval Required? Yes	No
6.	Change in supplier for a body material (after completion of a PDP or approval of a PMA). If a sponsor can demonstrate that the body material from the new supplier is chemically identical to the material from the present supplier with similar types and quantities of extractable from an exhaustive extraction, testing from the following sections of the guidance document should be performed and submitted: • mechanical (for single-piece models); • optical; and • biocompatibility. Note - Cytotoxicity is the only necessary toxicity test if the long-term safety of the material from the new supplier as body material can be supported by the ophthalmic literature. This testing should be performed even if the new material has been shown to be chemically equivalent to the material from the present supplier.		
	For single-piece lenses, if the mechanical behavior of the new material qualifies as a Level A modification, prior approval from FDA is not necessary.		X
	If the mechanical behavior of the new material fails to qualify as a Level A modification, a Level B clinical study should be performed and prior FDA approval is required. Multi-piece lenses are not expected to be affected by a change in the supplier of a body material.	X	
	If the material from the new supplier cannot be demonstrated to be chemically identical, then the testing recommended for changes in body material (see above) should be performed and the results submitted to FDA and approval obtained prior to implementation.	X	
7.	Addition of a new or different ultraviolet (UV) absorber. A change to a UV absorber that, when combined with the current base body material, has well-documented safety in the ophthalmic literature, should be qualified by performing the testing from the following sections of this guidance document: • optical; • biocompatibility;	X	

	Modification and Recommended Testing	Prior Approval Required? Yes	No
	• shelf life and shipping (specifically, product stability); and • clinical (Level B study). Note - Certain tests may be waived with a scientific rationale. A change to a UV absorber that does not have well-documented safety in the ophthalmic literature or for which safety information is not available on its combination with the current body base material, should be qualified by performing the testing recommended above, but with a full 300 subject clinical study.		
8.	Any change that affects safety and effectiveness and that is not addressed in this guidance or an approved PDP protocol.	X	

D. Clinical Trial Changes

	Modification and Recommended Testing	Prior Approval Required? Yes	No
1.	Multiple designs incorporated in a single clinical investigation (prior to completion of a PDP or completion of an IDE). A single material may be investigated with more than one design, if all the designs in the investigation have been previously qualified by being associated with parent models. Therefore, the only variable being investigated is the new material. The only restriction is that the mechanical properties of the parent lens should not be significantly altered (i.e., greater than a Level A modification) by being manufactured from the new material.	X	
2.	Multiple materials incorporated in a single clinical investigation (prior to completion of a PDP or completion of an IDE). A single design may be investigated with more than one loop, body, or single-piece material if all of the materials in the clinical investigation have been previously qualified by being associated with parent models. Therefore, the only variable being investigated is the new design. The only restriction is that if more than one material is used for the loops, all of the models should be Level A modifications of each other in terms of mechanical properties.	X	
3.	Change in clinical protocol that may affect the scientific soundness of the study or the rights, safety and welfare of the study subjects (21 CFR 812.35(a)).	X	

E. Technology or Performance Changes

A draft format for reporting manufacturing and quality control/quality assurance process changes is included in Annex E.

Modification and Recommended Testing	Prior Approval Required? Yes	No
1. Equipment changes Installation of new or improved equipment should be validated by performing an installation qualification and by demonstrating that the equipment produces a product that passes both in-process quality control testing and final release specifications. The effects of these changes should also be controlled through the Quality Systems Regulation (QSR).		X
2. Process Changes Process changes should be qualified with testing appropriate to the specific change. If the changes have been qualified to the device's current specifications and/or an FDA recognized guidance document or standard, and raise no new issues of safety or effectiveness, FDA approval prior to implementation is not necessary. Examples of common changes and recommended testing are listed below:		
a. Cleaning process changes • SEM • cytotoxicity • SEM/EDXA or IR • extractables and hydrolytic stability • exhaustive extraction, if the solvent is likely to be absorbed into the lens		X
b. Haptic formation process changes • mechanical testing • dimensions • cytotoxicity, if the new process involves the use of a processing aid that has not been previously qualified by the sponsor in a similar use		X
c. Haptic staking changes or the addition of primers or adhesives • dimensions • pull testing • exhaustive extraction (cytotoxicity testing may be required if the levels of extractables are higher or the identities of the extractables are different after the modification) • cytotoxicity, if the new process involves the use of a primer or adhesive that has not been previously qualified by the sponsor in a similar use • extractables and hydrolytic aging (not required if the change is purely mechanical in nature)		X

	Modification and Recommended Testing	Prior Approval Required? Yes	No
d.	Annealing or secondary manufacturing process changes that could reasonably be expected to affect the safety or effectiveness of the finished product. The following tests should be performed as appropriate: • mechanical testing • optical testing • exhaustive extraction • cytotoxicity • extractables and hydrolytic stability • Nd:YAG testing Sponsors may wish to contact FDA for guidance on specific changes.	X	
e.	Blocking or molding compound changes • SEM/EDXA • Cytotoxicity • extractables and hydrolytic stability		X
f.	Change to shelf life of raw materials or processing aids <u>Raw materials:</u> • complete chemical characterization (of the raw material) • IR (on the raw material and finished product) • exhaustive extraction (on the raw material and finished product) • cytotoxicity (on the finished product) (If the identity and levels of extractables are unchanged, cytotoxicity tests do not need to be performed.) • physical characterization (tensile strength, optical quality, etc. on the finished product) <u>Processing aids:</u> • visual inspection • IR, as appropriate		X
g.	Tumbling parameters or tumbling slurry changes • visual inspection by SEM for surface finish • SEM/EDXA, if a slurry component has a metallic element • cytotoxicity (if the sponsor does not have approval for the use of the new slurry for a device made of a similar material) • extractables and hydrolytic stability (not required for changes in tumbling time) • exhaustive extraction, if a new component of the slurry is likely to be absorbed into the lens If metal particles on the lens are detected by EDXA, a justification for the modification should be submitted and prior FDA approval is required.	X	X
h.	Change in sampling for quality control testing • if reduced number of samples, rationale for reduction, such as historical records, etc.		X

Modification and Recommended Testing	Prior Approval Required?	
	Yes	No
i. Change in quality audit procedure • explanation and rationale for the change		X
j. Editorial or clarification change to standard operating procedure (SOP) • explanation and rationale for the change		X
k. Change from a manual to an automated process for a final release inspection.	X	
All other changes from a manual to an automated process.		X
l. Quality control specification or process/method changes • Validation is specific to the QC parameter (sponsors may wish to consult FDA's guidance document "Modifications to Devices Subject to Premarket Approval" for further guidance on these changes)	Depends on the change.	

F. Sterilization/Packaging Changes

Sterilization changes should be qualified with testing appropriate to the specific changes. Examples of changes and recommended testing are listed in the table below.

Modification and Recommended Testing	Prior Approval Required?	
	Yes	No
1. New sterilization site. If a new sterilization site is being implemented, prior FDA approval is not necessary if the following apply: • the new site has been FDA inspected and the inspection has been classified by FDA as anything other than "OAI" (official action indicated); • the same (with respect to Installation Qualification/Commissioning Specifications) sterilization equipment is utilized; and • the same sterilization cycle parameters, as previously approved for the sterilization of the product, are being used at the new site.		X
In any of the previously listed conditions does not apply, prior FDA approval is necessary.	X	
2. Change in load configuration. The new load configuration should undergo validation in accordance with the applicable ISO standard referenced in Section V of this document.		X
3. Change in incubation parameters for Biological Indicators (BIs). If the BIs' incubation period is shortened, the new incubation period should be validated in accordance with "CDRH Guidance for Validation of Biological Indicator Incubation Time," June 5, 1985.		X

	Modification and Recommended Testing	Prior Approval Required?	
		Yes	No
4.	Change in environmental monitoring. The sponsor should provide a scientific or historical rationale for a change in the frequency or the alert/action levels in environmental monitoring.		X
5.	Change in sterilization cycle parameters. The new sterilization cycle should be validated in accordance with the applicable ISO standard referenced in Section V of this document. If the body and/or loop materials may be affected by the change in cycle parameters, the sponsor should ensure that the lenses sterilized with the new parameters still meet the current product specifications (e.g., dimensions). The sponsor should evaluate the effect of the change on aeration parameters (for ethylene oxide) and perform residuals testing, if necessary. Additionally, the sponsor should evaluate the effect of the change on the packaging and perform package integrity testing, if necessary.	X	
6.	Change in aeration conditions for ethylene oxide-sterilized IOLs. The IOLs should be subjected to residual testing in accordance with ISO 10993-7:1995.	X	
7.	Change in the concentration of ethylene oxide in the sterilant mixture. The sterilization cycle with the new sterilant mixture should be validated in accordance with ISO 11135; residuals testing on the IOLs should be performed in accordance with ISO 10993-7:1995. If the body and/or loop materials may be affected by the change in sterilant concentration, the sponsor should ensure that the lenses sterilized with the new parameters still meet the current product specifications (e.g., dimensions).	X	
8.	Change in the method of sterilization. The new sterilization cycle should be validated in accordance with the applicable ISO standard referenced in Section V of this document.	X	
9.	Installation of a different autoclave/sterilizer where different is defined as: • different (with respect to Installation Qualification/Commissioning specifications) sterilization equipment, i.e., a different brand or design of sterilizer, • different sterilization cycle parameters, or • different type of sterilization method. The new autoclave/sterilizer should be validated in accordance with the applicable ISO standard referenced in Section V of this document.	X	

Modification and Recommended Testing	Prior Approval Required?	
	Yes	No
10. Request for resterilization of finished lots of IOLs. The packaged IOLs should be subject to product and package integrity testing as outlined in Section VI of this document. If the IOLs are subjected to ethylene oxide, the IOLs should be subjected to residuals testing in accordance with ISO 10993-7:1995.	X	
11. Packaging material or design changes. Changes in packaging design or material composition should be qualified by demonstrating that the performance of the package (as established by the results of testing described in Section VI of this document) is not significantly different when compared to the original packaging. A revalidation of the sterilization cycle and/or aeration parameters is necessary for changes in package material, but may not be required for changes in package design with an appropriate scientific rationale. Performance testing of the IOL may be required. Additional guidance from FDA should be obtained regarding validation studies necessary to evaluate changes in package design or material. Guidance may also be obtained as to whether FDA approval is necessary prior to implementation. For example, a change in primary packaging from a single pouch to a double pouch should be validated by requalifying the sterilization cycle and aeration parameters. A change from a double pouch to a single pouch should be validated by performing package integrity and shipping testing.	Depends on the change.	

G. Shelf Life Extension

Modification and Recommended Testing	Prior Approval Required?	
	Yes	No
1. Extension of a product shelf life. The extension of a product shelf life should be validated by performing the testing described in Section VI of this document and/or an FDA approved protocol.		
If the extension of a product shelf-life has been validated according to an already approved protocol, the change does not require prior FDA approval.		X
Otherwise, FDA approval prior to implementation is required.	X	

H. Labeling Changes

Modification and Recommended Testing	Prior Approval Required? Yes	No
1. Editorial and/or format changes to the package insert or label. These changes should be documented.		X
2. Change to indications for use (additions or deletions). Sponsors should provide a rationale and supporting information if appropriate.	X	
3. Change to warning or precaution (additions or deletions).	X	
4. New claims. Sponsors should provide a rationale and supporting information. A clinical study may be necessary to support a new claim. Sample sizes for such a study should be determined based on safety and efficacy endpoints.	X	

I. Distributor Agreements

Recommended Information	Prior Approval Required? Yes	No
Sponsors who enter into a private distribution agreement with another firm should provide FDA with the following information regarding the agreement in a PMA supplement: 1. Distributor Name and Address 2. Will sponsor continue to market subject IOLs? 3. Trade Names and Model Numbers: The sponsor should provide the trade names and model numbers of both the sponsor and distributor. 4. Means by which sponsor will ensure traceability of lenses shipped to and implanted through distributor. 5. Statement that there will be no change in raw materials, manufacturing, processing, packaging, storage, specifications, or quality control of devices which were approved in PMA. If differences exist, the sponsor should state those differences. 6. If a specific post-approval follow-up was a condition of PMA approval, how this condition will be met.	X	

Recommended Information	Prior Approval Required?	
	Yes	No
7. How the following sponsor obligations will be fulfilled:		
a. 800 telephone number:		
b. Registration of Patients:		
c. ID card for patients:		
d. Restricted device: The distributor should agree to abide by all Conditions of Approval with respect to the distribution of devices and limitation of advertising claims to those contained in device labeling.		
e. Adverse reaction reporting and time frame with which sponsor will be notified by distributor.		
f. Annual report: Sponsor should describe arrangements with distributor for providing the sponsor with information on reportable events for inclusion in the sponsor's PMA annual reports.		
g. MDR reporting: Sponsor should describe who will be responsible filing adverse action and/or MDR reports.		
8. Labeling. Sponsor's and distributor's labeling should be provided. Except for company names, trade names, and model numbers, the distributor's labeling should be identical in content to the sponsor's, and include a statement "Manufactured for . . ." or "Distributed by . . ." (21 CFR 801.1(c).		

ANNEX A
(Normative)

SHELF-LIFE TEST TABLE

IOL Material		No. of finished IOL lots[1]	Dioptric power range	Tests per study type (minimum 10 IOLs per lot)		
Optic	**Haptics**			**Product stability**	**Package integrity[2]**	**Shipping stability[3]**
PMMA	PMMA	1	Medium	• Dimensions • Surface and bulk homogeneity	• Labeling • Seal integrity • Microbial barrier OR Whole package physical integrity	• Labeling • Surface and bulk homogeneity • Drop and vibration test • Seal integrity • Microbial barrier OR Whole package physical integrity
PMMA	Polypropylene, polyimide, or PVDF	1	Medium	• Dimensions • Surface and bulk homogeneity • Extractables[4] • Cytotoxicity[5]	• Labeling • Seal integrity • Microbial barrier OR Whole package physical integrity	• Labeling • Surface and bulk homogeneity • Drop and vibration test • Seal integrity • Microbial barrier OR Whole package physical integrity
Cross-linked polydimethyl-siloxane[6]	Cross-linked polydimethyl-siloxane, polypropylene, polyimide, PMMA, or PVDF	2	Low, Medium, High	• Dimensions • Folding/Injection testing[7] • Haptic pull test		
			Medium	• Surface and bulk homogeneity • Dioptric power • Imaging quality • Spectral transmission • Extractables[4] • Cytotoxicity[5]	• Labeling • Seal integrity • Microbial barrier OR Whole package physical integrity	• Labeling • Surface and bulk homogeneity • Drop and vibration test • Seal integrity • Microbial barrier OR Whole package physical integrity

IOL Material		No. of finished IOL lots[1]	Dioptric power range	Tests per study type (minimum 10 IOLs per lot)		
Optic	**Haptics**			**Product stability**	**Package integrity[2]**	**Shipping stability[3]**
Any other combination of optic and haptic materials not listed above		3	Low Medium High	• Dimensions • Dioptric power • Imaging quality • Folding/Injection testing (for foldable lenses)[7] • Haptic pull test		
			Medium (in addition)	• Surface and bulk homogeneity • Compression force • Dynamic fatigue testing • Extractables[4] • Cytotoxicity[5] • Spectral transmission • Specific surface tests (if warranted)	• Labeling • Seal integrity • Microbial barrier OR Whole package physical integrity	• Labeling • Surface and bulk homogeneity • Drop and vibration test • Seal integrity • Microbial barrier OR Whole package physical integrity

Notes:

1 Number of finished lots for product stability testing.

2 All package integrity testing should be performed on samples from the same finished lot(s). A minimum of three finished lots should be tested regardless of IOL material.

3 Only one lot of medium power IOLs is needed for shipping testing regardless of lens type.

4 For a description of a suitable extraction method, see Annex B of ISO/DIS 11979-6.

5 Cytotoxicity testing should be performed if an increase is seen in extractables content or if a new substance is present.

6 Sponsors may submit a rationale to support product stability testing on fewer than three lots for materials other than PMMA or cross-linked polydimethylsiloxane. The rationale should demonstrate that the material has a history of use in IOLs that have been produced by more than one manufacturer.

7 For a description of folding/injection testing, see the section of this guidance entitled "Mechanical Properties and Test Methods."

ANNEX B – FDA GRID OF HISTORICAL CONTROLS

Overall Visual Acuity (% ≥ 20/40)

Age	Posterior Chamber		Anterior Chamber – by Surgical Intent							
			Primary		Back-up		Secondary		All A/C Subjects	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
<60	230/235	**97.9**	94/102	**92.2**	13/16	**81.3**	59/65	**90.8**	166/183	**90.7**
60-69	968/1012	**95.7**	192/223	**86.1**	19/23	**82/6**	105/123	**85.4**	316/369	**85.6**
70-79	1793/1920	**93.4**	312/391	**79.8**	29/50	**58.0**	153/207	**73.9**	494/648	**76.2**
≥80	901/1042	**86.5**	165/233	**70.8**	15/30	**50.0**	70/101	**69.3**	250/364	**68.7**
Total*	3893/4210	**92.5**	763/949	**80.4**	76/119	**63.9**	387/496	**78.0**	1226/1564	**78.4**

Best Case Visual Acuity (% ≥ 20/40)

Age	Posterior Chamber		Anterior Chamber – by Surgical Intent							
			Primary		Back-up		Secondary		All A/C Subjects	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
<60	203/206	**98.5**	81/83	**97.6**	12/13	**92.3**	47/50	**94.0**	140/146	**95.9**
60-69	793/822	**96.5**	150/169	**88.8**	12/13	**92.3**	76/78	**97.4**	238/260	**91.5**
70-79	1338/1372	**97.5**	234/264	**88.6**	17/25	**68.0**	92/106	**86.8**	343/395	**86.8**
≥80	601/634	**94.8**	107/119	**89.9**	9/15	**60.0**	37/42	**88.1**	153/176	**86.9**
Total*	2936/3035	**96.7**	572/635	**90.1**	50/66	**75.8**	252/276	**91.3**	874/977	**89.5**

- The "Total" rates represent the rates associated with the distribution of subjects in the four age subgroups found in the historical control data. For a clinical study with different age distributions of subjects, the age-adjusted "Total" control rate should be calculated from the weighted average of the age subgroup rates in study.

Adverse Events

	Posterior Chamber		Anterior Chamber – by Surgical Intent							
			Primary		Back-up		Secondary		Total (A/C)	
#Cohort**	4219		952		119		496		1567	
# Core	5906		***		***		***		2197	
	n	%	n	%	n	%	n	%	n	%
Cumulative Hyphema	91	**2.2**	41	**4.3**	5	**4.2**	17	**6.9**	63	**4.0**
Cumulative Macular Edema	124	**3.0**	95	**10.0**	24	**20.2**	34	**1.2**	153	**9.8**
Cumulative Retinal Detachment	11	**0.3**	11	**1.2**	2	**1.7**	6	**0.6**	19	**1.2**
Cumulative Pupillary Block	5	**0.1**	19	**2.0**	3	**2.5**	3	**1.2**	25	**1.6**
Cumulative Lens Dislocation	5	**0.1**	10	**1.1**	5	**4.2**	6	**0.4**	21	**1.3**
Cumulative Endophthalmitis	4	**0.1**	2	**0.2**	0	**0.0**	2	**0.2**	4	**0.3**
Cumulative Hypopyon	16	**0.3**	***		***		***		4	**0.2**
Cumulative Surgical Reintervention	46	**0.8**	***		***		***		58	**2.6**
Persistent Macular Edema	19	**0.5**	36	**3.8**	11	**9.2**	16	**0.2**	63	**4.0**
Persistent Corneal Edema	11	**0.3**	5	**0.5**	2	**1.7**	11	**2.2**	18	**1.1**
Persistent Iritis	11	**0.3**	9	**0.9**	4	**3.4**	11	**1.8**	24	**1.5**
Persistent Raised IOP Requiring Treatment	17	**0.4**	20	**2.1**	10	**8.4**	9	**0.6**	39	**2.5**

** All adverse event rates except for cumulative hypopyon and cumulative surgical reintervention were derived from the cohort subjects. Hypopyon and surgical reintervention data were derived from all core subjects.

*** It was not possible to determine cumulative hypopyon and cumulative surgical reintervention rates by surgical intent for anterior chamber IOLs.

ANNEX C
(Informative)

SAMPLE PACKAGE INSERT

GENERIC LABELING RECOMMENDATIONS

Prescription Devices

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

Device Description

[Lens designation] are [ultraviolet-absorbing] [posterior/anterior] chamber intraocular lenses. They are designed to be positioned [posterior/anterior] to the iris where the lens should replace the optical function of the natural crystalline lens. However, accommodation will not be replaced.

Indications

[Lens designation] are generally indicated for primary implantation for the visual correction of aphakia in persons 60 years of age or older in whom a cataractous lens has been removed by [extracapsular cataract extraction or phacoemulsification]. The lens is intended to be placed in the [anterior chamber, ciliary sulcus, and/or the capsular bag].

Precautions

Do not attempt to resterilize the lens as this can produce undesirable side effects.

Do not soak or rinse the intraocular lens with any solution other than sterile balanced salt solution or sterile normal saline.

Do not store the lens in direct sunlight or at a temperature greater than [state validated storage temperature, XX °F/°C]. Do not autoclave the intraocular lens.

Warnings

Physicians considering lens implantation under any of the following circumstances should weigh the potential risk/benefit ratio:

1. Recurrent severe anterior or posterior segment inflammation or uveitis.

2. Patients in whom the intraocular lens may affect the ability to observe, diagnose, or treat posterior segment diseases.

3. Surgical difficulties at the time of cataract extraction which might increase the potential for complications (e.g., persistent bleeding, significant iris damage, uncontrolled positive pressure, or significant vitreous prolapse or loss).

4. A distorted eye due to previous trauma or developmental defect in which appropriate support of the IOL is not possible.

5. Circumstances that would result in damage to the endothelium during implantation.

6. Suspected microbial infection.

7. Children under the age of 2 years are not suitable candidates for intraocular lenses.

Adverse Events

The complications experienced during the clinical trial of Model [ ] include (in order of frequency): [list complications and adverse events].

Additional complications may include but are not limited to the following: [list additional complications that did not occur in clinical trial, but have been documented as occurring with the same type of IOL].

Adverse Events

[The standard FDA grid list of adverse events should be included for the complete study population and, if applicable, modified core population. Overall secondary surgery rates should be tabulated, as well as the rates by the reason for the secondary surgery. The data should be compared to the FDA grid results. In addition, the overall rate of adverse events as of the PMA data cut-off date should be provided, along with the overall number of implants.]

Statement: As of DATE, there were X Number implants and the overall incidence of reported adverse events is %.

Clinical Trial

Clinical trials of [Model(s) X] were initiated on [ ]. The results achieved by [XXX] patients followed for one year provide the basis for the data which were used to support that this IOL design can be used for the visual correction of aphakia.

Visual Acuity

[Report in tabular format the best case visual acuity at 12 -14 months postoperatively. The data should be tabulated by age decade and a category for 20/40 or better visual acuity should be provided. The number of subjects in each age decade should be included. Best case should be defined (i.e., patients with no preoperative ocular pathologies or macular degeneration at any time during the study). The data should be compared to FDA "grid" results.]

Detailed Device Description

Optic Material:
Power:
Index of Refraction:
UV transmittance 10% cutoff: (include curve)
Haptic Material: (specify one- or three-piece)

Directions for Use

1. Prior to implanting, examine the lens package for type, power, and proper configuration.
2. Open the peel pouch and remove the lens in a sterile environment.
3. Examine the lens thoroughly to ensure particles have not become attached to it, and examine the lens optical surfaces for other defects.
4. The lens may be soaked in sterile balanced salt solution until ready for implantation.

Caution: Do not use lens if the package has been damaged. The sterility of the lens may have been compromised.

Lens Power Calculations

The physician should determine preoperatively the power of the lens to be implanted. Lens power calculation methods are described in the following references:

Hoffer, K.J., "The Hoffer Q formula: a comparison of theoretic and regression formulas," Journal of Cataract and Refractive Surgery, Vol. 19, pp. 700-712, 1993; ERRATA, Vol. 20, pp. 677, 1994.

Holladay, J.T., Musgrove, K.H., Prager, T.C., Lewis, J.W., Chandler, T.Y., and Ruiz, R.S., "A three-part system for refining intraocular lens power calculations," Journal of Cataract and Refractive Surgery, Vol. 14, pp. 17-24, 1988.

Holladay, J.T., "Standardizing Constants for Ultrasonic Biometery, Keratometry and Intraocular Lens Power Calculations"; Journal of Cataract and Refractive Surgery, Vol. 23, pp. 1356-1370, 1997.

Norrby, N.E.S., "Unfortunate Discrepancies," Letter to the Editor and Reply by Holladay, J.T., Journal of Cataract and Refractive Surgery, Vol. 24, pp. 433-434, 1998.

Olsen, T., Olesen, H., Thim, K., and Corydon, L., "Prediction of pseudophakic anterior chamber depth with the newer IOL calculation formulas," Journal of Cataract and Refractive Surgery, Vol. 18, pp. 280-285, 1992.

Retzlaff, J.A., Sanders, D.R., and Kraff, M.C., "Development of the SRK/T intraocular lens implant power calculation formula," Journal of Cataract and Refractive Surgery , Vol. 16, pp. 333-340, 1990; ERRATA, Vol. 16, pp. 528, 1990.

Physicians requiring additional information on lens power calculation may contact [ ].

Patient Registration Section

[In addition to the usual company-specific information regarding registration procedures for their IOLs, this section should state clearly that the implant identification card must be given to the patient.]

Reporting

Adverse events and/or potentially sight-threatening complications that may reasonably be regarded as lens-related and that were not previously expected in nature, severity, or degree of incidence should be reported to [ ] at TOLL-FREE #. This information is being requested from all implant surgeons in order to document potential long-term effects of intraocular lens implantation.

How Supplied

[ ] are supplied sterile in a [ ] package. The package is sterilized with [ ] and should be opened only under sterile conditions.

Expiration Date

The expiration date on the lens package is the sterility expiration date. This lens should not be implanted after the indicated sterility expiration date.

Return/Exchange Policy

[The company's return policy regarding lenses past their sterility expiration date should be stated.]

Bibliography

[Sponsors should include updated and relevant references (e.g., references on lens calculations, complications, lens-specific surgical technique, etc.). It is not necessary to repeat references already included elsewhere in the label.]

LENS SPECIFIC RECOMMENDATIONS

Posterior Chamber IOLs

Warning
[The following should be added to the list of circumstances for which the physician should weigh the risk/benefit ratio under Warning:]
Patients in whom neither the posterior capsule nor zonules are intact enough to provide support.

Studied in Capsular Bag Only

Warnings
Since the clinical study of Model [ ] was conducted with the lens being implanted in the capsular bag only, there are insufficient clinical data to demonstrate its safety and efficacy for placement in the ciliary sulcus.

Anterior Chamber IOLs

Sizing Guidance
[These data should be included in the "Detailed Device Description" section of the labeling or in a "Mechanical Characteristics" section immediately following the detailed device description. The sizing guidance should specify whether the corneal diameter (white-to-white measurement) or the anterior chamber diameter (approximately 1 mm greater than the corneal diameter) should be used in selecting the appropriate lens diameter.]

Mechanical Characteristics
[These data should be included in the "Device Description" section of the labeling or in a "Mechanical Characteristics" section immediately following the description. Items 1, 2, and 3 should be included for non-rigid anterior chamber models which are available with lengths differing in 0.5 mm increments. Items 1, 2, 4, 5, and 6 should be included for anterior chamber models available with lengths differing by greater than 0.5 mm (includes 1-size-fits-all).

The longest and the shortest sizes available for each anterior chamber model should be tested under each item (e.g., "1. The force required to compress the diameter of the anterior chamber intraocular lens 0.5 mm: 1.5 gm (11.5 mm) - 1.2 gm (14.0 mm)"). At least 6 samples should be tested and the average value reported for each size. Labeling for rigid anterior chamber models (i.e., those which require greater than 50 gm to compress the diameter of the anterior chamber model 0.5 mm) need not include these mechanical characteristics.]

1. The force required to compress the diameter of the anterior chamber IOL 0.5 mm: [ ] gm.

2. The force required to compress the diameter of the lens 0.5 mm less than the original diameter after it has been compressed 0.5 mm for 24 hours at 37 °C in saline: [ ] gm.

3. The vault observed after compressing the diameter of the lens 1.5 mm: [ ] mm. The force required to compress the lens 1.5 mm: [ ] gm.

4. The force required to compress the diameter of the lens the maximum, amount expected in clinical usage: [ ] gm at [ ] mm of compression.

5. The force required to compress the diameter of the lens the maximum amount expected in clinical usage (from the original diameter) after it has been compressed this distance for 24 hours at 37°C in saline: [ ] gm.

6. The vault observed after compressing the diameter of the lens the maximum amount expected in clinical usage and adding 1.0 mm: [ ] mm. The force required to compress the lens that amount: [ ] gm.

Indications

The lens is indicated for implantation following:

1. primary intracapsular cataract extraction or
2. primary extracapsular cataract extraction provided that this be performed after the physician has compared the published results or his/her own results with Model [ ] series lenses with posterior chamber lenses or
3. primary extracapsular cataract extraction where there is a structural reason that a Model [ ] series lens is preferred (back-up use) or
4. secondary procedure in an aphakic patient.

Warnings

One or more iridectomies at the time of lens implantation may prevent the need for secondary iridectomies for pupillary block.

Under certain circumstances, there may be a slightly higher risk of implantation with an anterior chamber IOL. Therefore, patients with only one eye with potentially good vision should be approached with reasonable precaution.

[The following should be added to the list of circumstances for which the physician should weigh the risk/benefit ratio under Warnings:]

Corneal endothelial dystrophy
Glaucoma
Active chronic anterior or posterior uveitis
Rubeosis iridis
Synechiae
Short anterior segment

Clinical Data

[Visual acuity data should be presented for patients at 1-year post-operatively. Data should be tabulated separately for patients from the following groups:

Primary intracapsular cataract extraction (ICCE) with pre-operative/operative problems
Primary ICCE without pre-operative/operative problems
Primary extracapsular cataract extraction (ECCE)
Secondary implantation
Overall

Adverse event data should also be listed this way if warranted by the data (e.g., if any complication exceeds the FDA grid rate).]

Three-Year Postoperative Data

[Sponsors should update their package insert with the three year data.]

Cross-linked polydimethylsiloxanes and other soft materials

Directions for Use
[Recommend a folder/inserter with which the lens model(s) have been validated.]

Other soft materials

Light Transmittance
[A graph in the package insert which describes spectral transmittance should include a curve for a 20 diopter IOL or the highest and lowest power IOLs. A cut-off wavelength of 10% transmittance should be provided for the curve. The cut-off should also be included in the "Detailed Device Description" section of the labeling.

The spectral transmittance curve should be obtained from measurements either through blanks corresponding to the thickness of the central 3 mm of the 20 diopter IOL or the highest and the lowest power IOLs, or through the central 3 mm of actual IOLs. A recording spectrophotometer should be used with an air sample for reference, using the same 3-mm diameter aperture used during the IOL measurement. Alternative methods may be used, but the sponsor should demonstrate the equivalence to measuring the IOL or the blank.

The spectral transmittance graph should also contain the spectral transmittance curve for the phakic eye of a 53 year-old person. The wavelength range of the spectral transmittance curve should be 300 nm to 700 nm, recorded continuously or at no more than 5 nm increments.]

Reference: Boettner, E.A. and Wolter, J.R., "Transmission of the Ocular Media," Investigative Ophthalmology, 1:776-783, 1962.

Non-UV-Absorbing

Caution: This lens does not significantly absorb ultraviolet light in the range of 320 to 400 nanometers.

Surface Modified Lenses

[No claims should be made unless the sponsor has performed a study that substantiates the claim(s) and has obtained FDA approval. Data supporting the claim(s) may be required in the labeling.]

Small Optic (< 5.5 mm)

Warning
Small amounts of lens decentration occurring with an IOL having a narrow or small optic (< 5.5 mm) may cause glare or other visual disturbances under certain lighting conditions. Surgeons should consider this potential complication before implanting an IOL with a small or narrow optic.

Lenses manufactured with CFCs and other Class I ozone Depleting Materials

Warning

[EPA regulations require each product containing or manufactured with CFCs, halons, carbon tetrachloride, and methyl chloroform to bear the following warning statement:]

> WARNING: [Contains/Manufactured with] [insert name of substance], a substance which harms public health and environment by destroying ozone in the upper atmosphere.

[For devices that provide patient labeling and physician labeling, FDA has published optional additional language in the Federal Register of June 29, 1993 (58 FR 34812) that should accompany device products. For patient labeling, the warning statement should read as follows:]

> Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs) [or name of other class I substance, if applicable].
>
> > This product [contains/is manufactured with] [insert name of substance], a substance which harms public health and environment by destroying ozone in the upper atmosphere.
> >
> > Your physician has determined that this product is likely to help your personal health. USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR PHYSICIAN. If you have any questions about alternatives, consult with your physician.

[For the package insert for the physician, the warning statement should state that:]

> Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs) [or name of other class I substance, if applicable].
>
> > WARNING: [Contains/Manufactured with] [insert name of substance], a substance which harms public health and environment by destroying ozone in the upper atmosphere. A notice similar to the above WARNING has been placed in the information for the patient of this product pursuant to EPA regulations.

High (>34 D) and Low (<4 D) IOLs

Warning (for low power lenses only)

These lenses are not intended for correction of refractive error for phakic patients who do not have a cataract.

Precaution

Special consideration should be given to the dimensions of lenses at the extreme ends of the power range (> 34D, < 4 D) in relation to the anatomical clearances in the patient's eye. The potential impact of factors such as optic central thickness, optic edge thickness, and overall lens size on the patient's long-term clinical outcome should be carefully weighed against the potential benefit associated with the implantation of an intraocular lens. This is particularly true for anterior chamber lenses. The patient's clinical progress should be carefully monitored.

ANNEX D
(Informative)

FORMAT FOR REPORTING LENS MODIFICATIONS

A. General

The formats described below are suggested formats. Alternative reporting formats are permitted if appropriately justified. The omission of any required information should also be justified.

Testing and data analysis should be performed according to methods described in an approved test protocol.

The data should demonstrate that the properties of the modified IOL are not significantly different from those of parent model(s). The modifications to the parent lens should be within those described as Level A modifications in ISO/DIS 11979-7.

B. Engineering Drawings

Engineering drawings of the modified lens(es) should be labeled with optic diameter, overall diameter, loop angulation and sagitta, haptic caliber, materials (both optic and haptic), and lens model number. The engineering drawing should clearly depict optic shape factor, position of tabs, positioning holes, and/ or notches.

The engineering drawings of the parent lens(es) should have been included with the approved testing protocol.

C. Qualification of Design Attributes

The following table lists the attributes of the modified lens(es) which should be qualified by a parent lens(es) by reference and/ or by submission of mechanical data.

Modification	Requires Reference to Parent	Requires Mechanical Data
Optic Material	X	X
Haptic Material	X	X
Ridge on posterior surface	X	
Overall Diameter		X
Haptic Caliber		X
Haptic Configuration		X
Addition of Notches to Haptic		X

D. Comparison to a single parent model

Data for modified lens(es) should be reported in tabular format similar to that shown below. Comparison to the parent model may be done either by use of numerical data reported in

tabular format or by use of a plot of UFB/AC and LFB/AC for both the modified lens and the parent model for each compressed diameter and condition.

Parameter	Measure			
	10 mm*		11 mm**	
	Before Decay	After Decay	Before Decay	After Decay
Mean Force (x 10^{-5} N)	X	X	X	X
standard deviation (s.d.)	X	X	X	X
UFB	X	X	X	X
LFB	X	X	X	X
AC	X	X	X	X
UFB/AC	X	X	X	X
LFB/AC	X	X	X	X
Decentration	X		X	
s.d.	X		X	
Mean + 2 s.d.	X		X	
Tilt	X		X	
s.d.	X		X	
Mean + 2 s.d.	X		X	

* For lenses indicated for placement in capsular bag

** For lenses indicated for placement in ciliary sulcus

All cells with X indicate input required.

E. Comparison to multiple parent models

Data for modified lens(es) should be reported in tabular format (as depicted above). Comparison to the parent models should be done in a plot of parental mechanical data. The compression forces (UFB and LFB) should be plotted as a function of the angle of contact (AC) for each compressed diameter and condition. The parent boundary range should be created from only the data from those 2 parent models (within 30 ° of each other) that will be used for the comparison to the modified lens.

ANNEX E
(Informative)

FORMAT FOR REPORTING MANUFACTURING AND QUALITY CONTROL/ASSURANCE

A. General

The formats described below are suggested formats. Alternative reporting formats are permitted if appropriately justified. The omission of any required information should also be justified.

B. Flow Chart

A flow chart of the manufacturing and quality control/assurance processes should include the titles and document numbers for the standard operating procedures (SOPs). The flow chart should include all processes from receipt of raw material to release of packaged product.

C. Manufacturing SOPs

Copies of the manufacturing SOPs should be organized according to their placement in the flow chart.

D. Quality Control/Assurance SOPs

Copies of the quality control/assurance SOPs should be organized according to their placement in the flow chart.

E. Modifications

Modifications to manufacturing or quality control/assurance processes should include testing as recommended in the modification section of this guidance. The flow chart and SOPs should be revised to reflect modifications.

ANNEX F
(Informative)

STANDARDS AVAILABILITY

The final ANSI and ISO standards referenced in this guidance document are available from ANSI at the address below.

For hard-copy publications:

Global Engineering Documents
15 Inverness Way East
Englewood, CO 80112
tel: 800/ 854-7179 or 303/ 397-7956
fax: 303/ 397-2740
email: global@ihs.com
www: http://global.ihs.com

Requests for electronic delivery of standards can be submitted via ANSI's Electronic Standards Store at:

http://webstore.ansi.org
email: info@ansi.org

You may also call or fax ANSI at the following numbers for electronic delivery of a standard:

tel: 212/ 642-4931
fax: 212/ 398-0023

The ISO IOL draft standards referenced in this guidance document are currently at the DIS and FDIS level and are not available from ANSI. They may be obtained from the ISO Central Secretariat at the following address:

ISO Central Secretariat
1, rue de Varembé,
Case Postale 56, CH-1211
Genève 20, Switzerland,
Tel +41 22 749 01 11
Sales department: Fax +41 22 734 10 79
e-mail: sales@isocs.iso.ch
ISO homepage: http://www.iso.ch